Noninvasive ventilation strategies for patients with severe or critical COVID-19

A rapid evidence review of clinical outcomes

Date of Literature Search: 5/15/2021
Date of Submission: 9/6/2021

Prepared By:
Shannon E. Kelly, University of Ottawa Heart Institute
Becky Skidmore, Independent Information Scientist
George Wells, University of Ottawa Heart Institute

UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA

Declarations of Interests

None declared.

Acknowledgments

The authors would like to acknowledge Vijay Shukla, Shuching Hsieh, and Nathan Orr for their contributions to this rapid evidence report. We would also like to acknowledge our patient/citizen partners Elaine Zibrowski and Maya Sterne for their review and feedback on our protocol and their ongoing support for knowledge translation activities.

Funding Acknowledgement(s)

The Strategy for Patient-Oriented Research Evidence Alliance (SPOR EA) is supported by the Canadian Institutes of Health Research (CIHR) under the Strategy for Patient-Oriented Research (SPOR) initiative.

This project was funded in part by the World Health Organization (PO 202642154).

This project was funded in part by an in-kind contribution from the Cardiovascular Research Methods Centre at the University of Ottawa Heart Institute.

General Disclaimer

This report was prepared by the Cardiovascular Research Methods Centre of the University of Ottawa Heart Institute on behalf of the SPOR Evidence Alliance. It was developed through the analysis, interpretation, and synthesis of scientific research assessments published in peer-reviewed journals, institutional websites, and other distribution channels. It also incorporates selected information provided by experts and patient/citizen partners with lived experience on the subject matter. This document may not fully reflect all the scientific evidence available at the time this report was prepared. Other relevant scientific findings may have been reported since completion of this synthesis report.

The SPOR Evidence Alliance and the project team make no warranty, express or implied, nor assume any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, data, product, or process disclosed in this report. Conclusions drawn from or actions undertaken on the basis of, information included in this report are the sole responsibility of the user.

Protocol/Topic Registration:

This rapid evidence review was registered with the National Collaborating Centre for Methods and Tools (NCCMT) in May 2021 (https://www.nccmt.ca/covid-19/covid-19-evidence-reviews/428)

Table of Contents

Abbreviations

AHRF	acute hypoxemic respiratory failure
ARDS	acute respiratory distress syndrome
BiPAP	bilevel positive airway pressure
CPAP	continuous positive airway pressure
HFNC	high flow nasal cannula
HFNO	high flow nasal oxygen
IMV	invasive mechanical ventilation
MA	meta-analysis
NIV	noninvasive mechanical ventilation
NMA	network meta-analysis
NPPV	negative positive pressure ventilation
ROB	risk of bias
RCT	randomized controlled trial
RR	rapid review[1]
SOT	standard oxygen therapy
SR	systematic review
WHO	World Health Organization

[1] RR abbreviation in Summary of Findings tables represents a relative risk/risk ratio

KEY FINDINGS FROM THE RAPID EVIDENCE REVIEW

We located four RCTs reporting outcomes of interest in hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not needing emergent intubation (direct PICO).

In hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not needing emergent intubation, high flow nasal oxygen and continuous positive airway pressure ventilation may decrease mortality, invasive mechanical ventilation, and hospital or intensive care unit length of stay compared to standard oxygen therapy but findings are based on low quality of evidence.

Helmet noninvasive ventilation probably decreases invasive mechanical ventilation (moderate quality of evidence) but may increase patient discomfort compared to high flow nasal oxygen (low quality of evidence). Helmet noninvasive ventilation may decrease mortality and hospital or intensive care unit length of stay compared to high flow nasal oxygen but findings are based on low quality of evidence. We are uncertain whether continuous positive airway pressure ventilation increases or decreases mortality, invasive mechanical ventilation, and hospital or intensive care unit stay compared to high flow nasal oxygen.

We located 22 RCTs reporting outcomes of interest in hospitalized patients with acute respiratory distress syndrome (ARDS) and acute hypoxemic respiratory failure (AHRF) not needing emergent intubation (indirect PICO).

Additional data were available to compare helmet and facemask noninvasive ventilation and helmet and facemask continuous positive airway pressure for some outcomes, but evidence was not available for all comparisons of interest.

Compared to standard oxygen therapy:

- High flow nasal oxygen probably decreases mortality at 28 days, invasive mechanical ventilation and hospital length of stay (moderate quality of evidence).
- Facemask noninvasive ventilation probably decreases mortality at 30 days, invasive mechanical ventilation, and hospital or intensive care unit length of stay (moderate quality of evidence).
- Helmet continuous positive airway pressure may decrease in-hospital mortality and IMV but increase hospital length of stay (low quality of evidence).
- Facemask continuous positive airway pressure may decrease IMV and hospital length of stay (low quality of evidence) but we are uncertain whether in-hospital mortality is increased or decreased.

Compared to high flow nasal oxygen:

- Facemask noninvasive ventilation may increase mortality at 90 days, invasive mechanical ventilation and intensive care unit length of stay (low quality of evidence).

Helmet noninvasive ventilation may reduce mortality at 90 days and at one year, and hospital length of stay compared to facemask noninvasive ventilation (low quality of evidence).

PICO = population, intervention, comparator, outcome

1. Background for the rapid evidence review

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged at the end of 2019 as a novel coronavirus, resulting in a current global pandemic of respiratory illness, Coronavirus Disease 2019 (COVID-19).

- Severe and critical COVID-19 involves acute hypoxemic respiratory failure requiring oxygen and ventilation therapies.

- Clinical management of COVID-19 using ventilation strategies involves either supplemental oxygen therapy (SOT), high-flow nasal oxygen (HFNO), continuous positive airways pressure (CPAP), noninvasive positive pressure ventilation (NIV), and invasive mechanical ventilation (IMV), or possible a combination of more than one strategy.

- COVID-19 patients may deteriorate very quickly. The case fatality rate for patients with COVID-19 admitted to the intensive care unit (ICU) and receiving IMV varies, but is high[41] and avoiding progression to IMV is a common goal in hospitalized patients with COVID-19.

- A summary of available RCT evidence for use of NIV for hospitalized patients with severe or critical COVID19 and acute hypoxemic respiratory failure who do not need IMV is required to inform WHO COVID-19 Clinical Practice Guidelines.

- In the absence of high certainty evidence for hospitalized patients with COVID-19 and acute hypoxemic respiratory failure, evidence for hospitalized patients with acute respiratory distress syndrome and acute hypoxemic respiratory failure may also be informative to the WHO COVID-19 Clinical Practice Guideline panel.

2. Rapid evidence review approach for the direct PICO

Research question

In patients with severe or critical COVID-19, to what extent does high flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) impact the need for invasive mechanical ventilation (IMV), hospital length of stay, and death compared to standard oxygen therapy (SOT) or against each other?

Methods overview

We conducted a rapid review of the evidence for noninvasive ventilation strategies and implemented the population, intervention, comparator, outcomes (PICO) framework to formulate the research question (Table 1):

Table 1: PICO framework

Population	Hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not needing emergent intubation[a]
Intervention	• High flow nasal oxygen • Continuous positive airway pressure (facemask or helmet) • Noninvasive ventilation via facemask (or other non-helmet interfaces including nasal, oronasal and full facial mask) • Noninvasive ventilation via helmet
Comparators	• Standard oxygen therapy • Any intervention
Outcomes	**Primary:** Mortality (within 30, 60, 90 days, and longer if data available), need for invasive mechanical ventilation, hospital length of stay **Secondary:** Intensive care unit length of stay **Patient-identified outcomes of interest:** Patient comfort, satisfaction with care
Eligible study designs	Systematic/rapid reviews[b] to identify eligible trials, randomized controlled trials[c]

a-patients weaned off IMV or who require respiratory support following IMV are not in scope.
b-eligible SR/RRs had to directly address ventilation support for two or more interventions/comparators in the PICO.
c-eligible RCTs had to directly compare two or more interventions/comparators in the PICO and at least one outcome.

Table 2 provides a summary of the methods used for this rapid evidence assessment. Additional details on the approach to the rapid evidence review are provided in Appendix A.

Table 2: Summary of Methods

Search (systematic review/rapid reviews) *May 2-3, 2021*	Systematic/rapid reviews used to identify eligible trials Targeted search of COVID-19 meta-databases • WHO COVID-19 database • Living Overviews of Evidence (L.OVE) platform • COVID-END inventory of best evidence syntheses for clinical management
Search (randomized controlled trials) *May 15, 2021*	Top-up of recent RCTs published since date of last systematic review/rapid review search • WHO COVID-19 register • Cochrane COVID-19 register • Clinicaltrials.gov • International Clinical Trials Registry Platform[a] (Citation tracking and included references checked July 29, 2021)
Screening and selection	Single reviewer screened records using Covidence When they met the population, intervention, comparator, outcome: • Completed randomized controlled trials from systematic/rapid reviews were included in this review • Completed randomized controlled trials identified during the top-up search were included in this review
Data tabulation	Single reviewer with checking by a second reviewer Study characteristics and reported outcome data carried forward from the systematic/rapid reviews where possible • Top-up randomized controlled trials extracted *de novo*
Quality/ROB	Single reviewer with checking by a second Systematic/rapid reviews rapidly assessed using 'Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2' tool Randomized controlled trial risk of bias assessments were retrieved and carried forward for eligible randomized controlled trials from the systematic/rapid reviews New randomized controlled trials with no previous risk of bias assessment were rapidly appraised by single reviewer with checking by a second and assisted by RobotReviewer[b]
Synthesis	Meta-analysis (pairwise for each primary and secondary outcome) Descriptive synthesis of patient-identified outcomes

Summary of findings	Single reviewer with checking by a second reviewer Summary of Findings tables created with focus on indirectness, imprecision and risk of bias
Involvement of citizen partners	Reviewed and provided input on the population, intervention, comparator, and outcome. Added patient-reported outcomes. Review and co-author related report sections. Co-produce a patient-specific knowledge translation product

a: Planned but not executed due to availability of the database.
b: https://www.robotreviewer.net/ (last accessed Aug 4, 2021). Use of this software was planned but not executed due to availability of the application.

3. Rapid evidence review findings for the direct PICO

We located **four randomized controlled trials (RCTs)**[1-4] of noninvasive ventilation strategies in hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not requiring emergent intubation.

This evidence was collected using the included study lists of **three relevant systematic reviews**[29-33]**, four rapid reviews,**[34-37] **and a top-up search** of bibliographic databases for more recent RCTs.

The available evidence for noninvasive ventilation strategies is summarized using Summary of Findings tables for the direct PICO.

PICO = population, intervention, comparator, outcome

Identified systematic reviews

Three SRs reported in five records were identified[29-33].

1. ***Schünemann et al. (2020)*** completed a living systematic review (LSR) published as a systematic review and two additional research letters reporting updated results (current to July 2020)[29-31]. No additional updates have been published. This LSR addresses multiple research questions and streams of evidence, of which their reported PICO #1 is directly relevant to the benefits and harms of ventilation techniques for coronavirus infections, including those that causing COVID-19. The LSR had a protocol registered in advance and uses recognized SR methods and comprehensively searched 21 bibliographic databases. It was rated as a methodologically rigorous systematic review following assessment with AMSTAR2. The authors' noted in their conclusions that that direct studies in COVID-19 are limited and poorly reported based mostly on observational evidence in SARS, MERS and COVID-19. **The LSR (update #1) identified one completed RCT** published in April 2020 that followed patients (n=72) in the Huanggang hospital in China who were randomized to HFNC (n=37) or SOT (n=35) in patients with severe COVID-19 pneumonia and acute respiratory failure[3]. **Of the eight potentially relevant in-progress RCT records identified in the Schünemann et al. LSR, one additional RCT (RECOVERY-RS) is complete as of August 4, 2021, and has results available**. Results from the RECOVERY-RS trial are published in preprint (not peer-reviewed) format and are included in this rapid evidence review[2]. **One additional RCT[1] was identified using the reference list of the RECOVERY-RS pre-print publication.**

2. ***Agarwal et al. (2020)*** completed a rapid SR updating a previous SR and meta-analysis by Rochwerg et al.(2019) comparing HFNO to SOT for two unique research questions, one of which was relevant to our PICO[33]. No protocol was registered or published. Although this SR was completed in 7 days, a search of three bibliographic databases was completed (May 2020), and standard systematic review methods were utilized. The study received a moderate rating for methodological rigour using AMSTAR2, with downgrading in the rating attributable to details that were not reported in the publication pertaining to the rationale for selection criteria, not providing reasons for excluded studies, and no investigation of publication or funding biases. **This rapid**

SR did not find any RCTs that directly evaluated HFNC in patients with COVID-19 or other coronavirus infections, and studies in progress were not sought or reported.

3. ***Lewis et al. (2020)*** completed a Cochrane Systematic Review using best practice methods for SRs (rated as a rigorously conducted SR following assessment with AMSTAR2)[32]. The review updated a previously published Cochrane review that compared the use of HFNO to other types of NIV (SOT, NIV, or NIPPV, or BiPAP and CPAP) in adults requiring support to breathe in an ICU. Patients with COVID-19 were not the direct focus of the SR, but RCTs of COVID-19 patients were eligible for inclusion if implemented in the ICU setting and the patients included required respiratory support. **None of the 31 included studies evaluated HFNC, NIV or CPAP in patients with COVID-19**. None of the ongoing studies identified (n=51) as in-progress included patients with COVID-19.

Identified rapid reviews

Four additional rapid reviews using a range of accepted 'rapid review' methods were identified for inclusion[34-37]. Three RRs[35-37] were completed between March and November 2020, and one was published in May 2021[34]. **No RCTs directly evaluating the use of noninvasive ventilation strategies (HFNC, NIV, or CPAP) in COVID-19 patients were identified from the RRs.** Most reported results were from non-randomized studies or observational cohorts. One potentially relevant ongoing RCT comparing helmet CPAP to SOT was identified, but no results were published or posted to the study registration as of August 01, 2021 (NCT04326075).

Results from the top-up search

A top-up search (for literature published between 1 July 2020 and 15 May 2021) **identified one RCT of helmet NIV compared to HFNO in patients with COVID-19** (HENIVOT)[4]. Two RCTs in progress (COVIDNOCHE [NCT04381923] and NCT04507802) and one RCT (now identified as terminated) comparing helmet CPAP to HFNO were also located in the top-up search[42]. Of the 847 potentially relevant study registration records retrieved, none reported RCTs relevant to the PICO that were reported to be complete with results available.

Evidence from identified randomized controlled trials

Study characteristics and outcome data were extracted from the four completed RCTs[1-4] identified. Each RCT studied noninvasive ventilation support in hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure (AHRF) not requiring emergent intubation. A brief summary of each study is provided in Table 3. Additional details for the study and participant characteristics are reported in Table B1 and Table B2, Appendix B. Evidence tables are provided in Tables B3 to B14 in Appendix B.

Table 3: Brief summary of included RCTs

Study/Design	Population	Country/Setting	Interventions	Outcomes reported
Li et al. 2020[3] two-arm, parallel RCT N=72	Patients with severe coronavirus pneumonia complicated with acute respiratory failure	China, isolation ward of a single centre	HFNO [n=37] Standard oxygen therapy [n=35]	Mechanical ventilation at 12 h No patient-reported outcomes
Grieco et al. 2021[4] HENIVOT two-arm, parallel RCT N=109	Patients admitted to the intensive care unit with COVID-19–induced moderate to severe hypoxemic respiratory failure	Italy, ICUs in four centres	Helmet NIV [n=55] HFNO [n=54]	Intubation, 28 d Hospital LOS ICU LOS Patient-reported: Device-related discomfort
Perkins et al. 2021[2] RECOVERY-RS three-arm, adaptive RCT N=1272	Hospitalized adults with acute respiratory failure due to COVID-19 were deemed suitable for tracheal intubation if treatment escalation was required	United Kingdom, 75 hospitals	CPAP [n=380] HFNO [n=417] Standard oxygen therapy [n=475] (primary comparisons were CPAP to standard oxygen and HFNO to standard oxygen)	Mortality, 30 d Intubation, 30 d Tracheal intubation during the study period Critical care (ICU) LOS Hospital LOS No patient-reported outcomes
Teng et al. 2021[1] two-arm, parallel RCT N= 22	Patients diagnosed with severe COVID-19.	China, single centre	HFNO [n=12] Standard oxygen therapy [n=10]	Mortality (indirect) Hospital LOS ICU LOS No patient-reported outcomes

d=days; h=hours; HFNO=high flow nasal oxygen; ICU=intensive care unit; LOS=length of stay; RCT=randomized controlled trial; QoL=quality of life.

Evidence tables for mortality (30, 60, 90 days or longer), invasive mechanical ventilation, hospital LOS and ICU LOS are provided in Appendix B. Where appropriate and feasible, data were synthesized, and results are reported in Summary of Findings tables (Tables 4 to 7).

The risk of bias for each trial was assessed using the Cochrane risk of bias tool[43]. There was limited information regarding the assessed risk of bias to carry forward from the individual RCTs from the SR/RRs, and so de novo risk of bias assessments were completed (Figure B1, Appendix B). Mortality and intubation/IMV outcomes were considered in the assessment of blinding at the participant and

personnel level, and intubation specifically was considered when blinding of outcome assessment was assessed. Detailed assessments for each study are provided in Appendix B.

The Li et al. was published in simplified Chinese and was assessed by a reviewer fluent in that language. Both the Li et al. and Teng et al. studies failed to report information to inform assessments of random sequence generation, and Teng et al. also did not provide details regarding allocation concealment. Therefore, both studies are at unclear risk of selection bias. Teng et al., in particular, used vague language to describe how eligible patients were included and excluded from the study. Exclusion of participants was judged to be appropriate, but a further description of 'eliminated participants' includes:

> *"patient (sic) could not cooperate with and tolerate HFNC oxygen therapy; pneumothorax occurred during the treatment; the patient needed invasive mechanical ventilation during the treatment; the patient could not continue the treatment due to their deterioration during the course of treatment; the patient was unable to participate in the whole trial."*

Based on the descriptions provided, it is possible that additional patients were randomized to the HFNO group and then later excluded from the RCT after treatment had started, as authors state that some patients did not tolerate the therapy or needed invasive mechanical ventilation while on HFNO. No additional details are provided, and intubation outcomes are not reported as a study outcome. The authors report that all participants completed the study (which could be inferred as zero deaths in both study arms), but this assumption is at unclear risk of bias due to the participant eligibility and inclusion reporting deficits (unclear risk of attrition bias).

Participants and personnel were not blinded in any of the included RCTs, and blinding would have been difficult or impossible due to the nature of the interventions. Varying criteria may have been used within or across studies to initiate IMV. Intubation outcomes in the Grieco et al. RCT were independently adjudicated by external experts, but no adjudication of the intubation outcomes was reported in Teng et al. or Li et al. Perkins, Li and Teng et al. report that there was no blinding of outcome assessors.

In Greico et al. the reported primary outcome (days free of respiratory support at 28 days) differs from the planned primary outcome defined in the protocol (reintubation within 72 hours after extubation or at ICU discharge). In addition, some of the secondary outcomes reported were not described in the registered protocol, and some planned outcomes were not reported at all with no rationale to support (mortality at 90 days, quality of life).

Perkins et al. was assessed to be at a low risk of bias for all domains but unclear for IMV owing to lack of blinding and masking, which introduces the possibility that bias could be introduced by knowledge of treatment allocation through administration of interventions. Data are reported in a preprint (non-peer reviewed manuscript), and at the time of this rapid evidence review, have not been peer-reviewed. As such, data for longer-term outcomes are not yet reported/available, and it is unclear if any outcomes were adjudicated (this was not planned in the protocol). Direct comparisons of study outcomes between the HFNO and CPAP arms were not made in the RECOVERY-RS trial and not all study participants were eligible to be randomized to both arms in this pragmatic study due to the availability of the study interventions at various research sites.

Crossover or progression to other interventions or study arms and cointerventions could not be fulsomely assessed in the included RCTs, and therefore the risk of bias is unclear. Intention to treat data are extracted where available, but the resulting effects may be the result of a combination of therapies in some patients.

Patient-reported outcomes

One RCT[4] described patient-reported discomfort as measured by the Visual Analog Scale (VAS) in exploratory analyses. In the HENIVOT study, discomfort using VAS was 3.7 (SD 3.1) in the helmet group vs 1.8 (SD 2.4) in the high-flow nasal oxygen group (mean difference, 1.9 [95% CI, 1.4-2.5]; P < .001).

4. Summary of findings tables for the direct PICO

Note that not all RCTs included for each comparison report all outcomes.

HNFO vs SOT

Three RCTs compared HFNO to standard oxygen therapy and reported outcomes of interest[1-3]. Not all RCTs reported all outcomes.

Table 4: Summary of Findings table for HFNO compared to SOT

Population: Hospitalized patients with severe or critical COVID 19 and AHRF not needing emergent intubation
Intervention: HFNO
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates SOT	 HFNO	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality, 30 d	Relative risk**: 0.95 (CI 95% 0.75 - 1.19)** Based on data from 807 patients in 2 studies	**195** per 1000	**185** per 1000 Difference: **10 fewer per 1000** (CI 95% 49 fewer - 37 more)	**Low** Due to serious imprecision, inconsistency[1]	HFNO may decrease mortality at 30 days
IMV	Relative risk**: 0.96 (CI 95% 0.81 - 1.13)** Based on data from 854 patients in 2 studies	**395** per 1000	**379** per 1000 Difference: **16 fewer per 1000** (CI 95% 75 fewer - 51 more)	**Low** Due to serious inconsistency, imprecision[2]	HFNO may decrease IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 804 patients in 2 studies	**16.85** days Mean	**16.34** days Mean Difference: **0.51 fewer** (CI 95% 3.65 fewer - 2.55 more)	**Low** Due to serious imprecision and inconsistency[3]	HFNO may decrease hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 804 patients in 2 studies	**7.2** days Mean	**6.99** days Mean Difference: **0.21 fewer** (CI 95% 2.0 fewer - 1.58 more)	**Low** Due to serious imprecision and inconsistency[4]	HFNO may decrease ICU LOS

1. **Inconsistency: serious.** Point estimates vary widely (One RCT not estimable due to zero events in both study arms); **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals;
2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 67%.; **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals;
3. **Risk of Bias: no serious.** One RCT high risk of selection bias. Second RCT has unclear risk of bias for LOS due to no reported outcome denominators in largest study. Estimates were calculated using denominators from other study reported outcomes (incomplete data), Incomplete data and/or large loss to follow up; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 65%; **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals, Wide confidence intervals;
4. **Risk of Bias: no serious.** One RCT high risk of selection bias. Second RCT has unclear risk of bias for LOS due to no reported outcome denominators in largest study. Estimates were calculated using denominators from other study reported outcomes (incomplete data); **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 65%; **Imprecision: serious.** SD larger than mean.

CPAP vs SOT

One 3-arm RCT compared CPAP to standard oxygen therapy and reported outcomes of interest[2].

Table 5: Summary of Findings table for CPAP compared to SOT
Population: Hospitalized patients with severe or critical COVID 19 and AHRF not needing emergent intubation
Intervention: CPAP
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOT	CPAP		
Mortality, 30 d	Relative risk: **0.87 (CI 95% 0.64 - 1.18)** Based on data from 737 patients in 1 studies	**192** per 1000	**167** per 1000 Difference: **25 fewer per 1000** (CI 95% 69 fewer - 35 more)	**Moderate** Due to serious imprecision[1]	CPAP probably decreases mortality at 30 days
IMV	Relative risk: **0.81 (CI 95% 0.67 - 0.98)** Based on data from 733 patients in 1 studies	**413** per 1000	**335** per 1000 Difference: **78 fewer per 1000** (CI 95% 136 fewer - 8 fewer)	**Moderate** Due to serious imprecision[2]	CPAP probably decreases IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 737 patients in 1 studies	**17.3** days Mean	**16.34** days Mean Difference: **0.96 fewer** (CI 95% 3.59 fewer - 1.67 more)	**Moderate** Due to serious imprecision[3]	CPAP probably decreases hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 737 patients in 1 studies	**9.6** days Mean	**9.52** days Mean Difference: **0.08 fewer** (CI 95% 2.23 fewer - 2.07 more)	**Moderate** Due to serious imprecision[4]	CPAP probably has little or no difference on ICU LOS

1. **Inconsistency: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals, Only data from one study;
2. **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Only data from one study;
3. **Risk of Bias: no serious.** Unclear risk of bias for LOS due to no reported outcome denominators in largest study. Estimates were calculated using denominators from other study reported outcomes (incomplete data); **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals, Only data from one study;
4. **Risk of Bias: no serious.** Unclear risk of bias for LOS due to no reported outcome denominators in largest study. Estimates were calculated using denominators from other study reported outcomes (incomplete data); **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: serious.** Wide confidence intervals, only data from one study.

HELMET NIV vs HFNO

One 2-arm RCT compared helmet NIV to HFNO and reported outcomes of interest[4].

Table 6: Summary of Findings table for HFNO compared to hemlet NIV
Population: Hospitalized patients with severe or critical COVID 19 and AHRF not needing emergent intubation
Intervention: Helmet NIV
Comparator: HFNO

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		HFNO	Helmet NIV		
Mortality, 28 d	Relative risk: **0.8 (CI 95% 0.34 - 1.87)** Based on data from 110 patients in 1 study	**182** per 1000	**146** per 1000 Difference: **36 fewer per 1000** (CI 95% 120 fewer - 158 more)	**Low** Due to very serious imprecision[1]	Helmet NIV may decrease mortality at 28 days
Mortality, 60 d	Relative risk: **1.1 (CI 95% 0.55 - 2.2)** Based on data from 110 patients in 1 study	**236** per 1000	**260** per 1000 Difference: **24 more per 1000** (CI 95% 106 fewer - 283 more)	**Low** Due to very serious imprecision[2]	Helmet NIV may increase mortality at 60 days
IMV	Relative risk: **0.54 (CI 95% 0.32 - 0.89)** Based on data from 110 patients in 1 study	**509** per 1000	**275** per 1000 Difference: **234 fewer per 1000** (CI 95% 346 fewer - 56 fewer)	**Moderate** Due to serious imprecision[3]	Helmet NIV probably decreases IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 110 patients in 1 study	**22** days Median	**16** days Median Difference: **6 fewer** (CI 95% 14 fewer - 1 more)	**Low** Due to serious risk of bias, imprecision[4]	Helmet NIV may decrease hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 110 patients in 1 study	**10** days Median	**4** days Median Difference: **6 fewer** (CI 95% 13 fewer - 1 more)	**Low** Due to serious risk of bias, imprecision[5]	Helmet NIV may decrease ICU LOS
Device-related discomfort	Measured by: Scale: - Lower better Based on data from 110 patients in 1 study	**1.8** VAS points Mean	**3.7** VAS points Mean Difference: **1.9 higher** (CI 95% 1.4 higher - 2.5 higher)	**Low** Due to serious risk of bias, imprecision[6]	Helmet NIV may increase device-related discomfort
Mortality, 90 d	No studies were found that looked at mortality at 90 days[7]				

1. **Risk of Bias: no serious.** Selective outcome reporting; **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
2. **Risk of Bias: no serious.** Selective outcome reporting; **Indirectness: no serious.** Unclear influence of group crossover and co-interventions; **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;

3. **Imprecision: serious.** Only data from one study, Low number of patients;
4. **Risk of Bias: serious.** Incomplete data (medians/IQR by group reported with absolute difference in means compared); **Imprecision: serious.** Low number of patients, Only data from one study;
5. **Risk of Bias: serious.** Incomplete data (medians/IQR by group reported with absolute difference in means compared); **Imprecision: serious.** Low number of patients, Only data from one study;
6. **Risk of Bias: serious.** post hoc outcome assessment, multiple time points collected, but not reported; **Imprecision: serious.** Low number of patients, Only data from one study;
7. **Risk of Bias: very serious.** Selective outcome reporting (outcome planned but not reported).

CPAP vs HFNO

One three-arm pragmatic RCT reported outcomes for CPAP and HFNO[2] but did not compare these interventions directly in the planned analyses. All patients did not have the opportunity to be randomized to all arms due to the availability of these interventions by centre (thereby making direct comparison unfeasible). To inform the clinical guideline panel discussions, we have provided an exploratory estimate for CPAP compared to HFNO using an indirect treatment comparison (Table B15, Appendix B).

Table 7: Summary of Findings table for CPAP compared to HFNO
Population: Hospitalized patients with severe or critical COVID 19 and AHRF not needing emergent intubation
Intervention: CPAP
Comparator: HFNO

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		HFNO	CPAP		
Mortality, 30 d	Relative risk**: 0.95 (CI 95% 0.52 - 1.71)** Based on data from 793 patients in 1 study	**188** per 1000	**179** per 1000 Difference: **9 fewer per 1000** (CI 95% 90 fewer - 133 more)	**Very low** Due to serious risk of bias, indirectness, and imprecision[1]	We are uncertain whether CPAP increases or decreases mortality at 30 days
IMV	Relative risk**: 0.69 (CI 95% 0.43 - 1.09)** Based on data from 791 patients in 1 study	**411** per 1000	**284** per 1000 Difference: **127 fewer per 1000** (CI 95% 234 fewer - 37 more)	**Very low** Due to serious risk of bias, indirectness, and imprecision[2]	We are uncertain whether CPAP increases or decreases IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 791 patients in 1 study	**18.3** days Mean	**16.63** days Mean Difference: **1.67 fewer** (CI 95% 5.43 fewer - 2.09 more)	**Very low** Due to serious risk of bias, indirectness, and imprecision[3]	We are uncertain whether CPAP increases or decreases hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 791 patients in 1 study	**10.5** days Mean	**9.48** days Mean Difference: **1.02 fewer** (CI 95% 3.97 fewer - 1.93 more)	**Very low** Due to serious risk of bias, indirectness, and serious imprecision[4]	We are uncertain whether CPAP increases or decreases ICU LOS

1. **Risk of Bias: serious.** Incomplete data and post hoc comparison: CPAP and HFNO were not available to all study participants and this comparison was not made in the RCT.; **Indirectness: serious.** Direct comparisons not available; **Imprecision: serious.** Only data from one study;
2. **Risk of Bias: serious. Indirectness: serious.** Direct comparisons not available; **Imprecision: serious.** Only data from one study;
3. **Risk of Bias: serious. Indirectness: serious.** Direct comparisons not available; **Imprecision: serious.** Low number of patients, Only data from one study, Wide confidence intervals;
4. **Risk of Bias: serious. Indirectness: serious.** Direct comparisons not available; **Imprecision: serious.** Only data from one study.

Conclusions relevant to the direct PICO

In hospitalized patients with severe or critical COVID-19 and acute hypoxemic respiratory failure not needing emergent intubation, high flow nasal oxygen and continuous positive airway pressure ventilation may decrease mortality, invasive mechanical ventilation, and hospital or intensive care unit length of stay compared to standard oxygen therapy but findings are based on low quality of evidence.

Helmet noninvasive ventilation probably decreases invasive mechanical ventilation (moderate quality of evidence) but may increase patient discomfort compared to high flow nasal oxygen (low quality of evidence). Helmet noninvasive ventilation may reducemortality and hospital or intensive care unit length of stay compared to high flow nasal oxygen but findings are based on low quality of evidence. We are uncertain whether continuous positive airway pressure ventilation increases or decreases mortality, invasive mechanical ventilation, and hospital or intensive care unit stay compared to high flow nasal oxygen.

There are no studies reporting evidence for facemask or other oronasal NIV in hospitalized patients with severe or critical COVID-19 AHRF not needing emergent intubation. Findings of the included studies also generally showed clinical benefits with helmet NIV and CPAP over HFNO, notably for the reduction of IMV with helmet NIV, although more studies are needed to confirm these findings. The studies to-date likely use ventilation strategies in conjunction with other interventions (e.g., patient in prone position, medication) and must be considered with any benefits or harms. The anticipated additional outcomes from the RECOVERY-RS RCT may also provide important longer-term assessments to supplement the current evidence base. Studies currently underway will likely provide new information in mid- to late-2022.

5. Rapid Evidence review approach for the indirect PICO

Research Question

In patients with acute respiratory distress syndrome (ARDS) and acute hypoxemic respiratory failure (AHRF), to what extent does high flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) impact the need for invasive mechanical ventilation (IMV), hospital length of stay and death compared to standard oxygen therapy (SOT) or against each other?

Methods overview

Due to the uncertainty in the randomized controlled trial (RCT) evidence in severe or critical COVID-19 populations, we completed an additional rapid evidence review for noninvasive ventilation strategies in non-COVID patients with ARDS and AHRF. We implemented the population, intervention, comparator, outcomes (PICO) framework to formulate the research question (Table 8).

Table 8: PICO framework

Population	Patients hospitalized with acute respiratory distress syndrome and acute hypoxemic respiratory failure that do not require emergent intubation[a]
Intervention	• High flow nasal oxygen • Continuous positive airway pressure • Noninvasive ventilation via facemask (or other non-helmet interfaces including nasal, oronasal, and full facial mask) • Noninvasive ventilation via helmet
Comparators	Standard of care (conventional oxygen therapy) or any other intervention
Outcomes	**Primary:** Mortality (within 30, 60, 90 days, and longer if data available), need for invasive mechanical ventilation, hospital length of stay **Secondary:** ICU length of stay **Patient-identified outcomes of interest:** Patient comfort, satisfaction with care
Eligible study designs	Systematic/rapid reviews [b] to identify eligible trials, randomized controlled trials[c]

a-patients weaned off IMV or who require respiratory support following IMV are not in scope.
b-eligible SR/RRs had to directly address ventilation support for two or more interventions/comparators in the PICO.
c-eligible RCTs had to directly compare two or more interventions/comparators in the PICO and at least one outcome.

We followed a similar rapid evidence review approach as for hospitalized patients with severe or critical COVID-19 and AHRF, with differences summarized below in Table 9.

Table 9: Methods summary – Differences from direct PICO

Search (Systematic reviews/rapid reviews) ***May 18, 2021***	Systematic reviews/rapid reviews used to identify relevant randomized controlled trials A targeted search of meta-databases • Epistemonikos database[2] of systematic reviews for health decision-making (includes Cochrane reviews) • Living Overviews of Evidence (L.OVE) Platform
Search (randomized controlled trials) *May 19, 2021*	Top-up of recent randomized controlled trials published since date of last systematic/rapid review search • Clinicaltrials.gov • International Clinical Trials Registry Platform[a] • Cochrane CENTRAL (Citation tracking and included randomized controlled trial reference lists checked July 29, 2021) *Date of latest systematic review/rapid review search in included randomized controlled trials for top-up: December 1, 2020*

a: Planned but not executed due to availability of the database. COCHRANE CENTRAL searched instead as a post hoc study registry substitution.

[2] https://www.epistemonikos.org/en/about_us/methods

6. Rapid evidence review findings for the indirect PICO

We located **22 completed randomized controlled trials (RCTs)[5-26] in 24 reports[5-28]** of non-invasive ventilation support in hospitalized patients with acute respiratory distress syndrome (ARDS) and acute hypoxemic respiratory failure (AHRF) not requiring emergent intubation.

This evidence was collected using the included study lists of **four systematic reviews (SRs)[32,38-40]. A top-up search** of study registry databases found no eligible RCTs.

The available evidence for noninvasive ventilation strategies for the indirect PICO is summarized using Summary of Findings tables.

None of the included SRs included RCTs relevant to the indirect PICO with patient-reported outcomes such as comfort or satisfaction with care.

PICO = population, intervention, comparator, outcome

Identified systematic reviews

We identified four relevant SRs (included in 7 published reports)[32,38-40,44-46].

1. ***Ferreyro et al. 2020[39,45,46]*** completed a systematic review and network meta-analysis (NMA) examining noninvasive oxygenation strategies in adults with AHRF with a focus on mortality and intubation outcomes. “Studies that were primarily focused on the treatment of acute exacerbations of chronic obstructive pulmonary disease (i.e., >50% of the study population) or congestive heart failure (i.e., >50% of the study population) and those evaluating noninvasive oxygen strategies in the immediate post-extubation period and after major cardiovascular surgery were excluded”[39]. Methods were based on accepted SR approaches that were published in a protocol prior to execution. Limitations in the SR approach, as identified using the AMSTAR2 tool, include an unclear rationale for certain aspects of the methodology, not reporting an excluded study list and the assessment of publication bias. Methodology related to the NMA was not assessed. The search in this review is current to April 2020. A total of 25 RCTs were included. Most included RCTs compared facemask NIV to SOT (n=14), and not all included studies reported both mortality and intubation outcomes. Other included RCTs compared helmet NIV or HFNO to SOT or to each other; however, the RCTs comparing active interventions was limited. In this review, CPAP was pooled with noninvasive ventilation for all outcome comparisons. Results based on indirect comparisons showed a reduction in risk of death of endotracheal intubation with NIV strategies compared to SOT. Authors highlight the potential benefits of delivering NIV through a helmet interface, although low certainty should be considered when interpreting the results as findings are

based on limited evidence. No differences in the hospital or ICU LOS were noted for any intervention.

2. ***Yasuda et al. 2021***[38] conducted a SR and NMA of noninvasive respiratory support in acute respiratory failure with a focus on associations between short-term mortality and intubation rates. A protocol was registered in advance (CRD42020139105). The review included studies of noninvasive positive pressure ventilation (NPPV), HFNO and SOT, with BiPAP and CPAP included in the NIV intervention group for syntheses. Standard SR and NMA methodology were used, with limitations noted in the December 2020 search (no alternatives to database and study registry searching), unclear data extraction methodology, inclusion of only English or Japanese language studies and no reporting of publication bias assessment. Limited study characteristics were reported, and no excluded study references were provided with reasons. The funding of studies was not investigated. Methodology related to the NMA was not assessed. A total of 25 RCTs were included. The final analysis included 19 RCTs comparing NPPV to SOT, seven comparing HFNC and SOT and five comparing HFNC and NPPV. Differences in the number of included studies and partial overlap with the Ferreyro SR/NMA are due to the fact that this SR included studies of patients with CHF and >50% COPD while excluding studies of cardiac or abdominal surgery. This contributed to differences in findings for major outcomes compared to Ferreyro et al. and increased heterogeneity significantly in the NMA.

3. ***Baldomero et al. 2021***[40,44] conducted a SR on the effectiveness and harms of HFNO for acute respiratory failure. Standard SR methodology was used, and a protocol was registered in advance (CRD42019146691). Methods were briefly presented, but multiple bibliographic databases were searched up to July 2020. Interventions of interest were HFNO, SOT, NIV, and both pre- and post-extubation studies were included. Limitations of this SR were that the authors only included English-language studies and that methods were insufficient to conduct a fulsome assessment. A total of 29 RCTs (in 32 records) were included. Results indicated that HFNO may make little or no difference in all-cause mortality, intubation or hospital LOS compared to SOT, and data for ICU LOS is uncertain (in populations using interventions for initial management). Compared with NIV, HFNO may reduce intubation, all-cause mortality and improve patient comfort in initial acute respiratory failure management.

4. ***Lewis et al. 2021***[32] conducted a Cochrane Systematic Review using best practice methods for SRs[32]. The review updated a previously published Cochrane review that compared the use of HFNO to other types of NIV (SOT, NIV, or NIPPV, or BiPAP and CPAP) in adults requiring support to breathe in an ICU. Patients were eligible for inclusion if implemented in the ICU setting, and the patients included required respiratory support. Both pre and post-extubation RCTs were included in this review. A total of 31 RCTs were included that

evaluated HFNC, NIV or CPAP. This review concluded that "HFNC may lead to less treatment failure when compared to standard oxygen therapy, but probably makes little or no difference to treatment failure when compared to NIV or NIPPV. For most other review outcomes, we found no evidence of a difference in effect. However, the evidence was often of low or very low certainty."

Assessment of randomized controlled trial eligibility

After screening all individual RCTs included in the SRs (n=74), a total of 22 RCTs (in 24 reports)[5-28] matching our indirect PICO were included. Results from the syntheses and GRADE assessments from individual SRs could not be used for mortality, IMV, and hospital or ICU LOS as a number of studies were not relevant to this PICO. Results for individual RCTs of interest were not well-reported in the SRs, and so outcome data from each study was extracted *de novo*. Participant and study characteristics and ROB were carried forward where possible and supplemented through the extraction of additional relevant information.

RCTs identified from the SRs were excluded if they:

a) were post-extubation or weaning interventions;
b) contained ≥ 50% participants with COPD, abdominal or cardiac surgery, or CHF;
c) did not report an outcome of interest.

Results from the top-up search

A top-up search for literature published between 1 Dec 2020 and 1 June 2021, identified a total of 1926 records. No additional RCTs were eligible for inclusion.

Evidence from identified randomized controlled trials

Twenty-two RCTs reported in 24 records were identified[5-28]. Details on study characteristics and outcome data were extracted from the 22 RCTs identified (Tables C1 and C2, Appendix C). Evidence tables for mortality (30, 60, 90 days or longer), IMV, hospital LOS and ICU LOS are provided in Tables C3 through C20 in Appendix C. Where appropriate and feasible, data were synthesized. Where few RCTs reported mortality outcomes of interest, the longest reported mortality data were synthesized as exploratory post hoc outcomes. Results were used to inform the Summary of Findings tables (Tables 10 to 15) .

The risk of bias for each trial for mortality and IMV were carried forward from the SR. None of the SRs assessed risk of bias associated with LOS outcomes as these outcomes were generally secondary or exploratory outcomes. Mortality and intubation/invasive mechanical intubation outcomes were considered in the assessment of blinding at the participant and personnel level, and intubation specifically was the specific consideration when blinding of outcome assessment was considered. SRs differed in the way they rated risk of bias due to lack of blinding (unclear or high).

Hospital LOS data are difficult to interpret as competing risk for death may not have been appropriately accounted for in most RCTs. LOS outcomes are generally secondary or exploratory outcomes in the RCTs, and as such, all indications are that estimates are confounded by death, and LOS data for survivors and non-survivors are rarely presented separately. Data were insufficient to synthesize results for hospital or ICU LOS by survivors or non-survivors in this rapid evidence review (Tables C21 and C22, Appendix C).

Additional figures are available in Appendix C for the indirect PICO.

Patient-important outcomes from SRs

Ferreyro et al.[39] planned to synthesize meaningful results for prespecified secondary outcomes of patient comfort, but outcomes were only available in 28% of included studies and no syntheses or descriptive results were presented.

In Baldomero et al.[40] patient comfort outcomes based on percentage improved or VAS were reported in two included RCTs (872 participants), however patient populations were not relevant to the PICO as participants had COPD or were post-cardiothoracic surgery. Results in the Summary of findings tables suggested that HFNO may make little or no difference in patient comfort.

Lewis et al.[32] found no evidence of a difference in comfort according to the type of respiratory support used, although this conclusion is based on some RCTs not relevant to the PICO for this rapid evidence report.

Yasuda et al.[38] did not include any patient-reported outcomes.

7. Summary of Findings tables for the indirect PICO

Note that not all RCTs included for each comparison report all outcomes.

HNFO vs SOT[5,8,14,18,19,27]

Table 10: Summary of Findings table for HFNO compared to SOT (indirect PICO)

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: HFNO
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOT	HFNO		
Mortality, 28 d	Relative risk: **0.99 (CI 95% 0.82 - 1.19)** Based on data from 776 patients in 1 study	**361** per 1000	**357** per 1000 Difference: **4 fewer per 1000** (CI 95% 65 fewer - 69 more)	**Moderate** Due to serious imprecision[1]	HFNO probably decreases mortality at 28 days
Mortality, 90 d	Relative risk: **0.92 (CI 95% 0.63 - 1.32)** Based on data from 522 patients in 2 studies	**189** per 1000	**174** per 1000 Difference: **15 fewer per 1000** (CI 95% 70 fewer - 60 more)	**Low** Due to serious inconsistency, imprecision[2]	HFNO may decrease mortality at 90 days
IMV	Relative risk: **0.74 (CI 95% 0.56 - 0.99)** Based on data from 668 patients in 4 studies	**207** per 1000	**153** per 1000 Difference: **54 fewer per 1000** (CI 95% 91 fewer - 2 fewer)	**Moderate** Due to serious indirectness[3]	HFNO probably decreases IMV
Mortality, any[4]	Relative risk: **0.98 (CI 95% 0.83 - 1.15)** Based on data from 1344 patients in 4 studies	**291** per 1000	**285** per 1000 Difference: **6 fewer per 1000** (CI 95% 49 fewer - 44 more)	**Low** Due to serious indirectness, imprecision[5]	HFNO may decrease mortality
Hospital LOS	Measured by: Scale: - Lower better Based on data from 998 patients in 2 studies	**16.26** days Median	**15.09** days Median Difference: **1.17 fewer** (CI 95% 3.16 fewer - 0.83 more)	**Moderate** Due to serious imprecision[6]	HFNO probably decreases hospital LOS
ICU LOS	Based on data from 996 patients in 2 studies	Studies were not pooled		**Low** Due to very serious inconsistency[7]	HFNO may have little or no difference on ICU LOS

1. **Imprecision: serious.** Wide confidence intervals, Only data from one study;
2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 80%.; **Imprecision: serious.** Wide confidence intervals;
3. **Indirectness: serious.** Differences between the population of interest and those studied;
4. Longest duration mortality data available, includes mix of hospital and end of study (EOS) outcomes

5. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was moderate, with I^2: 44%.; **Indirectness: serious.** Differences between the population of interest and those studied (some mixed, some immunocompromised), Differences between the outcomes of interest (timing); **Imprecision: serious.** Wide confidence intervals;
6. **Imprecision: serious.** Wide confidence intervals;
7. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high, with I^2: 85%, the direction of the effect is not consistent between the included studies.

FACEMASK NIV vs SOT [6,10,13-17,20,24-27]

Table 11: Summary of Findings table for Facemask NIV compared to SOT (indirect PICO)

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Facemask NIV
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOT	Facemask NIV		
IMV	Relative risk: **0.74** **(CI 95% 0.64 - 0.86)** Based on data from 1166 patients in 10 studies	**416** per 1000	**308** per 1000 Difference: **108 fewer per 1000** (CI 95% 150 fewer - 58 fewer)	**Moderate** Due to serious inconsistency[1]	Facemask NIV probably decreases IMV
Mortality, 30 d	Relative risk: **0.88** **(CI 95% 0.62 - 1.25)** Based on data from 374 patients in 1 study	**273** per 1000	**240** per 1000 Difference: **33 fewer per 1000** (CI 95% 104 fewer - 68 more)	**Moderate** Due to serious imprecision[2]	Facemask NIV probably decreases mortality at 30 days
Mortality, 60 d	Relative risk: **0.7** **(CI 95% 0.31 - 1.58)** Based on data from 56 patients in 1 study	**357** per 1000	**250** per 1000 Difference: **107 fewer per 1000** (CI 95% 246 fewer - 207 more)	**Low** Due to very serious imprecision[3]	Facemask NIV may decrease mortality at 60 days
Mortality, 90 d	Relative risk: **0.87** **(CI 95% 0.58 - 1.3)** Based on data from 395 patients in 3 studies	**375** per 1000	**326** per 1000 Difference: **49 fewer per 1000** (CI 95% 158 fewer - 113 more)	**Very low** Due to serious inconsistency, indirectness, imprecision[4]	We are uncertain whether facemask NIV increases or decreases mortality at 90 days
Mortality, any	Relative risk: **0.83** **(CI 95% 0.71 - 0.96)** Based on data from 1254 patients in 11 studies	**347** per 1000	**288** per 1000 Difference: **59 fewer per 1000** (CI 95% 101 fewer - 14 fewer)	**Moderate** Due to serious indirectness[5]	Facemask NIV probably decreases mortality
Hospital LOS	Measured by: Scale: - Lower better Based on data from 829 patients in 6 studies	**20.51** days Median	**18.49** days Median Difference: **2.02 fewer** (CI 95% 4.39 fewer - 0.35 more)	**Moderate** Due to serious inconsistency[6]	Facemask NIV probably decreases hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 1152 patients in 10 studies	**9.43** days Median	**7.82** days Median Difference: **1.61 fewer** (CI 95% 3.21 fewer - 0.03 fewer)	**Moderate** Due to serious inconsistency[7]	Facemask NIV probably decreases ICU LOS

1. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 57%. Variation in timepoint IMV outcome was assessed at;

2. **Indirectness: no serious.** Differences between the population of interest and those studied (100% immunocompromised population); **Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
4. **Inconsistency: serious.** The magnitude of statistical heterogeneity was moderate, with I^2: 58%.; **Indirectness: serious.** Direct comparisons not made in one RCT and so crude data used to estimate the comparison; **Imprecision: serious.** Wide confidence intervals;
5. **Indirectness: serious.** Combined in-hospital and longer duration mortality at varying time points;
6. **Inconsistency: serious.** The magnitude of statistical heterogeneity was moderate, with I^2:55%;
7. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 75%.

HELMET CPAP vs SOT[9,11,23]

Table 12: Summary of Findings table for Helmet CPAP compared to SOT (indirect PICO)

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Helmet CPAP
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates SOT	 Helmet CPAP	Certainty of the Evidence (Quality of evidence)	Plain language summary
IMV	Relative risk: **0.45 (CI 95% 0.15 - 1.34)** Based on data from 168 patients in 3 studies	**102** per 1000	**46** per 1000 Difference: **56 fewer per 1000** (CI 95% 87 fewer - 35 more)	**Low** Due to serious inconsistency, imprecision[1]	Helmet CPAP may decrease IMV
In-hospital mortality	Relative risk: **0.23 (CI 95% 0.1 - 0.55)** Based on data from 168 patients in 3 studies	**250** per 1000	**58** per 1000 Difference: **192 fewer per 1000** (CI 95% 225 fewer - 112 fewer)	**Low** Due to serious indirectness, imprecision[2]	Helmet CPAP may decrease in-hospital mortality
Hospital LOS	Measured by: Scale: - Lower better Based on data from 81 patients in 1 study	**14** days Median	**14.5** days Median Difference: **0.5 more** (CI 95% 3.75 fewer - 4.75 more)	**Low** Due to very serious imprecision[3]	Helmet CPAP may increase hospital LOS
ICU LOS	No studies were found that looked at ICU LOS				

1. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 55%; **Imprecision: serious.** Low number of patients, Wide confidence intervals;
2. **Risk of Bias: no serious.** One trial stopped earlier than scheduled, potential for overestimating benefits; **Indirectness: serious.** One trial of patients with hematologic malignancies, Differences between the outcomes of interest (30d or longer) and those reported (in-hospital); **Imprecision: serious.** Low number of patients;
3. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

FACEMASK CPAP vs SOT[12]

Table 13: Summary of Findings table for Facemask CPAP compared to SOT (indirect PICO)

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Facemask CPAP
Comparator: SOT

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		SOT	Facemask CPAP		
In-hospital mortality	Relative risk**: 0.71 (CI 95% 0.38 - 1.32)** Based on data from 123 patients in 1 study	**295** per 1000	**209** per 1000 Difference: **86 fewer per 1000** (CI 95% 183 fewer - 94 more)	**Very low** Due to serious indirectness and very serious imprecision[1]	We are uncertain whether facemask CPAP increases or decreases in-hospital mortality
IMV	Relative risk**: 0.86 (CI 95% 0.54 - 1.37)** Based on data from 123 patients in 1 study	**393** per 1000	**338** per 1000 Difference: **55 fewer per 1000** (CI 95% 181 fewer - 145 more)	**Low** Due to very serious imprecision[2]	Facemask CPAP may decrease IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 81 patients in 1 study	**16** days Median	**14** days Median Difference: **2 fewer** (CI 95% 17.5 fewer - 13.5 more)	**Low** Due to very serious imprecision[3]	Facemask CPAP may decrease hospital LOS
ICU LOS	Measured by: Scale: - Lower better Based on data from 81 patients in 1 study	**9** days Median	**9** days Median Difference: **0 fewer** (CI 95% 8.89 fewer - 8.89 more)	**Low** Due to very serious imprecision[4]	Facemask CPAP may have little or no difference on ICU LOS

1. **Indirectness: serious.** Differences between the outcomes of interest (30d or longer) and those reported (in-hospital); **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
2. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
3. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
4. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

FACEMASK NIV vs HNFO[7,14,22]

Table 14: Summary of Findings table for Facemask NIV compared to HFNO (indirect PICO)

Population: hospitalized patients with ARDS and AHRF who do not need emergent intubation
Intervention: Facemask NIV
Comparator: HFNO

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		HFNO	**Facemask NIV**		
Mortality, 90 d	Relative risk: **2.3** **(CI 95% 1.27 - 4.15)** Based on data from 216 patients in 1 study	**123** per 1000	**283** per 1000 Difference: **160 more per 1000** (CI 95% 33 more - 387 more)	**Low** Due to very serious imprecision[1]	Facemask NIV may increase mortality at 90 days
IMV	Relative risk: **1.22** **(CI 95% 0.94 - 1.59)** Based on data from 316 patients in 3 studies	**364** per 1000	**444** per 1000 Difference: **80 more per 1000** (CI 95% 22 fewer - 215 more)	**Low** Due to serious risk of bias, imprecision[2]	Facemask NIV may increase IMV
In-hospital mortality	Relative risk: **1.15** **(CI 95% 0.55 - 2.43)** Based on data from 70 patients in 1 study	**265** per 1000	**305** per 1000 Difference: **40 more per 1000** (CI 95% 119 fewer - 379 more)	**Very low** Due to serious indirectness, very serious imprecision[3]	We are uncertain whether facemask NIV increases or decreases in-hospital mortality
Hospital LOS	No studies were found that looked at hospital LOS				
ICU LOS	Measured by: Scale: - Lower better Based on data from 216 patients in 1 study	**12.8** days Median	**13.35** days Median Difference: **0.55 more** (CI 95% 3.16 fewer - 4.26 more)	**Low** Due to very serious imprecision[4]	Facemask NIV may increase ICU LOS

1. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
2. **Risk of Bias: serious.** two of three trials have unclear sequence generation and concealment of allocation during randomization process (one abstract only at high risk of bias with incomplete data); **Imprecision: serious.** Low number of patients, Wide confidence intervals;
3. **Indirectness: serious.** Differences between the outcomes of interest (30d or longer) and outcome reported (in-hospital); **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study;
4. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

HELMET NIV versus FACEMASK NIV[21,28]

Table 15: Summary of Findings table for Helmet NIV compared to Facemask NIV (indirect PICO)

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Helmet NIV
Comparator: Facemask NIV

Outcome	Study results and measurements	Absolute effect estimates Facemask NIV	 Helmet NIV	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality, 90 d	Relative risk: **0.6 (CI 95% 0.37 - 0.99)** Based on data from 83 patients in 1 studies	**564** per 1000	**338** per 1000 Difference: **226 fewer per 1000** (CI 95% 355 fewer - 6 fewer)	**Low** Due to very serious imprecision[1]	Helmet NIV may decrease mortality at 90 days
Mortality, 1 yr	Relative risk: **0.62 (CI 95% 0.42 - 0.93)** Based on data from 83 patients in 1 studies	**692** per 1000	**429** per 1000 Difference: **263 fewer per 1000** (CI 95% 401 fewer - 48 fewer)	**Low** Due to very serious imprecision[2]	Helmet NIV may decrease mortality at 1 year
IMV	Relative risk**: 0.3 (CI 95% 0.15 - 0.58)** Based on data from 83 patients in 1 studies	**615** per 1000	**185** per 1000 Difference: **430 fewer per 1000** (CI 95% 523 fewer - 258 fewer)	**Low** Due to very serious imprecision[3]	Helmet NIV may decrease IMV
Hospital LOS	Measured by: Scale: - Lower better Based on data from 83 patients in 1 studies	**7.8** days Median	**4.7** days Median Difference: **5.1 fewer** (CI 95% 9.38 fewer - 0.82 fewer)	**Low** Due to very serious imprecision[4]	Helmet NIV may decrease hospital LOS
ICU LOS	No studies were found that looked at ICU LOS				

1. **Imprecision: very serious.** Low number of patients, Only data from one study;
2. **Imprecision: very serious.** Low number of patients, Only data from one study;
3. **Imprecision: very serious.** Low number of patients, Only data from one study;
4. **Imprecision: very serious.** Low number of patients, Only data from one study.

Appendix A: Detailed methods - Rapid evidence review for the direct PICO

Search

A targeted search was made of two electronic meta-databases (*WHO COVID-19 database and Living Overviews of Evidence (L.OVE) platform*) and the *COVID-END inventory of best evidence syntheses for clinical management* to rapidly identify eligible SR/RRs [May 2 to 3, 2021].

We used the identified SR/RRs to locate and include RCTs in this review and inform the start date for a 'top up' search for RCTs available after the most recent SR/RR. All RCT records identified in the SR/RRs as in progress or ongoing were checked for new results (July 15, 2021).

The 'top-up' search involved three electronic databases (*WHO COVID-19 register, Cochrane COVID-19 register, clinicaltrials.gov*) [May 15, 2021]. We planned a search of the International Clinical Trials Registry Platform (ICTRP), but the database was not accessible to our information scientist during this rapid evidence review. Reference lists and citation tracking of included SR, RR and RCTs was completed July 29, 2021

The complete search strategy is available by request.

Screening, selection and data extraction

All records were uploaded into EndNoteX20 and then into Covidence for screening and selection. One reviewer screened all records to identify eligible studies (SR/RRs and then RCTs). Included SR/RRs and RCTs directly compared two or more interventions/comparators in the PICO and reported at least one outcome. We excluded studies reporting broad clinical course as it is not possible to link clinical outcomes and isolate the effect of the ventilation strategy.

All study data were retrieved and carried forward from the SR/RRs or, when not reported, extracted *de novo* into structured outcome tables (Microsoft Excel) by a single reviewer with checking by a second reviewer.

Quality appraisal

Included SR/RRs were appraised using AMSTAR2.

Existing risk of bias (ROB) assessments were retrieved and carried forward when available for eligible RCTs from the SR/RRs. A single reviewer assessed the risk of bias in RCTs with no previous assessment or when the reported assessment from the SR/RRs was not informative for the summary of findings tables. A second review author checked the ROB. The Cochrane risk of bias tool was used (v1.0).

Synthesis

Pairwise-MA was conducted by comparison and outcome for eligible RCTs. Otherwise, a descriptive summary of evidence by comparison/outcome.

For comparisons of HFNO to CPAP, where the interventions were not directly compared in the RCT, relative effects were calculated in two ways: 1) by directly comparing the reported summary data by arm in pair-wise meta-analysis; and, 2) using the pooled relative effects (relative risk) from HFNO compared to SOT and CPAP

compared to SOT to calculate an indirect estimate for the relative effects of CPAP compared to HFNO. Both are reported in the summary of findings tables.

Hospital LOS data are difficult to interpret as competing risk for death may not have been appropriately accounted for in most RCTs. LOS outcomes are generally secondary or exploratory outcomes in the RCTs, and as such, all indications are that estimates are confounded by death, and LOS data for survivors and non-survivors is rarely presented separately.

Summary of findings tables

Summary of Findings tables were created by a single reviewer with complete checking by a second reviewer.

Appendix B: Detailed results - Rapid evidence review for the direct PICO

Summary of SR and RRs

Table B1: Systematic and rapid reviews used to identify relevant RCTs for the direct PICO

Included:	Population	Interventions studied	Outcomes reported	Search date	RCTs identified	AMSTAR2 rating
Systematic reviews						
Lewis et al. 2021[32], *Cochrane Systematic Review***	Adults (16 years or older) requiring support to breathe in an ICU	HFNC compared to other types NIV Including standard oxygen therapy, NIV, or NIPPV, or (BiPAP and CPAP)	Treatment failure, in-hospital mortality (up to 90d), ICU LOS, short- and long-term patient comfort.	17 April 2020	0 RCTs in COVID-19 pts 0 ongoing RCTs in COVID-19 pts	High quality
Schünemann et al. 2020[29-31a], *Annals of Internal Medicine*	Patients with confirmed or probable COVID-19 infection and hypoxemic respiratory failure	PICO 1: NIV, including Bi-PAP, CPAP, and HFNC; IMV; standard oxygen therapy; or no mechanical ventilation	death, IMV hospital LOS, ICU LOS, contextual outcomes (acceptability, feasibility, resources use, effect on equity)	Latest update 11 July 2020	0 RCTs in base LSR 1 RCT[3] in LSR update 1 0 RCTs in LSR Update 2 1 RCT[2] identified as in-progress with results available 1 RCT[1] identified using the reference list of an identified RCT	High quality

Included:	Population	Interventions studied	Outcomes reported	Search date	RCTs identified	AMSTAR2 rating
Agarwal et al. 2020[33]*, *Canadian Journal of Anaesthesia*	Critically ill COVID-19 patients with acute hypoxemic respiratory failure	HFNO compared to standard oxygen therapy, NIV, NIPPV (CPAP, BiPAP)	Mortality, IMV hospital LOS, ICU LOS	14 May 2020	0 RCTs in COVID-19 pts Did not report RCTs in-progress	Moderate Quality Identified as rapid but reporting brief, so assessment of quality limited
Rapid reviews						
Alberta Health Services, Alberta, Canada, 2020[37]	Acute Hypoxemic respiratory failure not due to AECOPD or CHF	Noninvasive ventilation, helmet CPAP, BiPAP	any	6 May 2020	0 RCTs in COVID-19 pts	Methods not reported, unable to assess
Swedish Agency For Health Technology Assessment and Assessment of Social Services 2020[35]	Acute respiratory failure due to coronavirus	'Noninvasive ventilation' CPAP, BiPAP, NIPPV, nasal ventilation, mask ventilation[b]	effectiveness	March 2020	0 RCTs in COVID-19 pts	Moderate quality
New South Wales Health, Evidence Check. Australia, 2020[36]	Patients with severe Covid-19	CPAP, BiPAP	any	1 and 6 April 2020	0 RCTs in COVID-19 pts 1 RCT in-progress[d]	Methods not reported, unable to assess
Radovanovic et al. 2021[34]	Patients with acute respiratory failure secondary to COVID-19 pneumonia	CPAP, NIV	In-hospital mortality	1 Nov 2020[c]	0 RCTs Did not report RCTs in-progress	Moderate to low quality

AHS=Alberta Health Services; CPAP=; BiPAP=Bilevel Positive Airway Pressure;

**Note that COVID-19 pts included in a subpopulation of adult intensive care patients (the population of interest for the review).
*Update of Rochwerg et al. 2019.
a: includes two published living updates. Multiple PICOs investigated. Data represented PICO 1 relevant to this rapid evidence review.
b: interventions identified from the provided search strategy.
c: limited specific search based on NIV and CPAP only, and in-hospital mortality.
d: EC-COVID-RCT (Helmet CPAP compared to standard oxygen, planned n=900, NCT04326075).

Summary of RCT study and participant characteristics: direct PICO

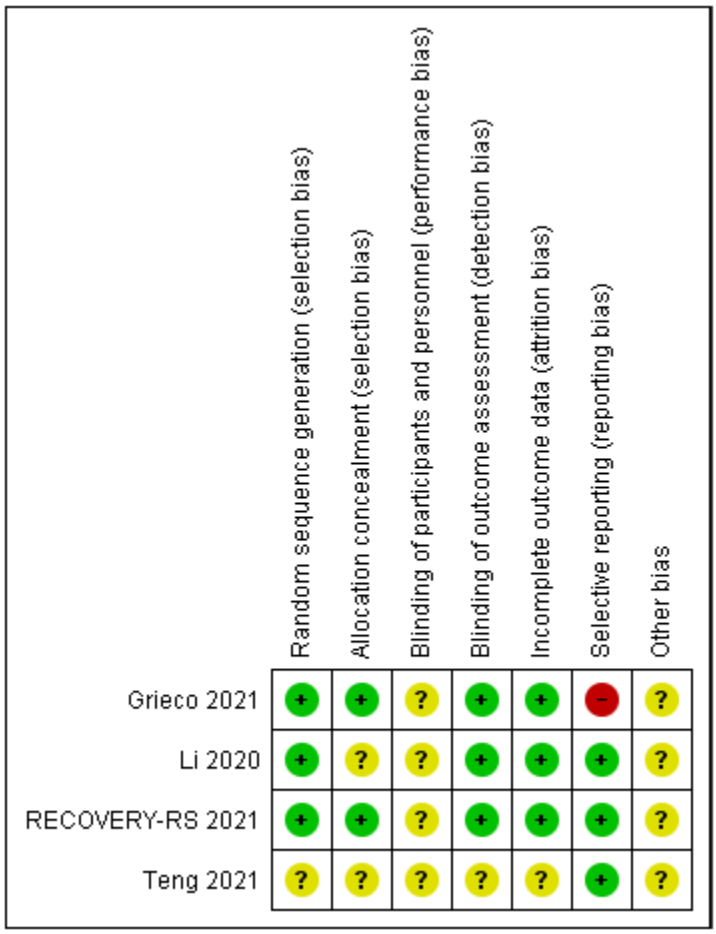
Table B2: Participant and study characteristics

Study/Design	Population	Interventions	Outcomes reported	Age (y), Mean±SD	PaO2.FiO2 ratio	Respiratory rate, /min	Funding
Li et al. 2020[3] two-arm, parallel RCT, CHINA (single centre) N=72	Patients with severe coronavirus pneumonia complicated with acute respiratory failure	HFNC [n=37] Standard oxygen therapy [n=35]	Mechanical ventilation at 12 h	HFNC 32±6.42 SOT 35±4.67	Not reported HFNC PaO2= 63.162 ±3.912 mmHg SOT PaO2=62.886 ±3.243 mmHg	Not reported	Unclear
Grieco et al. 2021[4] HENIVOT NCT04502576 two-arm, parallel RCT, ITALY (4 centres) N=109	Patients admitted to the intensive care unit with COVID-19–induced moderate to severe hypoxemic respiratory failure	Helmet NIV [n=55] HFNO [n=54]	Intubation, 28 d Hospital LOS ICU LOS	median (IQR) Helmet NIV 66 (57-72) HFNO 63 (55-69)	Helmet NIV 105 (83-125) HFNO 102 (80-124)	Helmet NIV 28 (24-32) HFNO 28 (23-32)	Funded by a research grant (2017 Merck Sharp & Dohme SRL award) by the Italian Society of Anesthesia, Analgesia, and Intensive Care Medicine
Perkins et al. 2021[2]	Hospitalized adults with acute respiratory	CPAP [n=380]	Mortality, 30 d	CPAP 56.7 ± 12.5	CPAP 131.8 ± 67.8	CPAP 26.4 ± 7.5	Funded and prioritized as

Study/Design	Population	Interventions	Outcomes reported	Age (y), Mean±SD	PaO2.FiO2 ratio	Respiratory rate, /min	Funding
RECOVERY-RS ISRCTN16912075 three-arm, open-label, adaptive RCT, UK (75 centres) N=1272	failure due to COVID-19 deemed suitable for tracheal intubation if treatment escalation was required	HFNO [n=417] Standard oxygen therapy [n=475] (primary comparisons were CPAP to standard oxygen and HFNO to standard oxygen)	Intubation, 30 d Tracheal intubation during study period Critical care (ICU) LOS Hospital LOS	 HFNO 57.6 ± 13.0 SOT 57.6 ± 12.7	 HFNO 138.5 ±87.6 SOT 134.9 ± 82.8	 HFNO 25.4 ± 7.0 SOT 25.0 ± 6.8	an urgent public health COVID-19 study by the National Institute for Health Research
Teng et al. 2021[1] two-arm, parallel RCT, CHINA (single centre) N= 22	Patients diagnosed with severe COVID-19	HFNO [n=12] Standard oxygen therapy [n=10]	“Cured and discharged” (100% so used to infer not death) Hospital LOS ICU LOS	HFNC 56.6 ± 3.0 SOT 53.5 ± 5.5	HFNC 224.25 ± 12.60 SOT 216.70 ± 4.62	HFNC 22.08 ± 0.70 SOT 21.60 ± 0.40	“The second batch of COVID-19 emergency science and technology project in Fuyang city (FK20202802)”

Risk of bias summary

Figure B1: Risk of bias assessments for included RCTs (direct PICO).



Detailed RCT ROB assessments

Teng et al. 2020

Domain/ Description	Quote supporting judgement	Judgement
Random sequence generation	"Of these patients, 12 were randomized assigned to the HFNC oxygen therapy group and 10 were randomized assigned to the conventional oxygen therapy (COT) group…". Methods for sequence generation not described.	Unclear
Allocation concealment	As above, method for allocation concealment not described.	Unclear
Blinding of participants and personnel	Blinding not reported and likely impossible due to the use of different apparatus/techniques. The participants' and	Unclear

	personnel's performance could have been biased due to their knowledge of the assigned treatment.	
Blinding of outcome assessors	Blinding not reported.	Unclear
Incomplete outcome data -mortality	--	Unclear
Incomplete outcome data- IMV	--	Unclear
Selective outcome reporting	No protocol was not found. However, the outcomes of interest are reported as planned in the methods section.	Low

Grieco et al. 2021

Domain/ Description	Quote supporting judgement	Judgement
Random sequence generation	"A computer-generated randomization scheme with randomly selected block sizes ranging from 3 to 9 managed by a centralized web-based system was used to allocate participants to each group."	Low
Allocation concealment	As above, a centralized web-based system was used. It was judged appropriate.	Low
Blinding of participants and personnel	"…an investigator-initiated, 2-group, open-label, multicenter, randomized clinical trial…" No blinding. The participants' and personnel's performance could have been biased due to their knowledge of the assigned treatment.	Unclear
Blinding of outcome assessors	"…Because the final decision on intubation was left to the physician in charge who could not be blinded to the study group, 2 independent experts blindly reviewed a posteriori the records and verified whether the decision to intubate was unbiased and in compliance with the required criteria. In case of disagreement between experts, a third physician established whether the criteria had been met." No blinding but the intubation intervention followed strict and objective criteria and retrospectively reviewed and verified in consensus.	Unclear (IMV not adjudicated, not used) Low (IMV adjudicated, mortality) Both outcomes were presented
Incomplete outcome data -mortality	"…intensive care unit mortality, in-hospital mortality, 28-day mortality, 60-day mortality…Ninety-day mortality and quality of life after 6 and 12 months were among the pre-specified secondary outcomes, but results are not reported." Mortality-related outcome assessment not likely influenced at all.	Low
Incomplete outcome data- IMV	As presented in figure 2, all randomized participants were included in the analysis except for two in the noninvasive ventilation helmet group and one in the high-flow nasal oxygen group, with the overall completion rate of 97% (107/110). It was judged to be at low risk of bias for incomplete outcome data.	Low
Selective outcome reporting	Protocol was registered (NCT02107183). However, the reported primary outcome, the number of days free of respiratory support (including high-flow nasal oxygen, noninvasive and invasive ventilation) within 28 days after enrollment", was different from what was pre-planned	High

	"Reintubation within 72 hours after extubation or at ICU discharge". Some of the secondary outcomes in the main publication were not described in the registered protocol, e.g., the number of days free of invasive mechanical ventilation at days 28 and 60. It was judged to be at high risk of reporting bias. Prespecified outcomes 90 mortality and quality of life not reported and no rationale provided.	

Li et al. 2020[3]

Domain/ Description	Quote supporting judgement (copy from article with quotation marks)	Judgement
Random sequence generation	"７２例新型冠状病毒肺炎并发急性呼吸衰竭患者，按随机数字表(random number table)法将患者分为观察组与对照组。" Random number table was used and judged to be appropriate.	Low
Allocation concealment	Method for **a**llocation concealment was not provided.	Unclear
Blinding of participants and personnel	Blinding was not reported and appeared infeasible due to the two treatments involving different apparatus /techniques. The participants' and personnel's performance could have been biased due to their knowledge of the assigned treatment.	Unclear
Blinding of outcome assessors	The outcome "intubation after 12-hour continuous treatment" was investigated but the criteria were not provided. The personnel's administration/decision of intubation could have been based on participant's signs and symptoms and clinical judgement.	Low
Incomplete outcome data -mortality	No mortality outcomes reported.	Low
Incomplete outcome data- IMV	It appeared that all randomized participants were followed to the end of the study. No attrition was reported.	Low
Selective outcome reporting	Protocol was not available. However, the reported outcomes appeared to match the methods section.	Low

Perkins et al. 2021

Domain/ Description	Quote supporting judgement (copy from article with quotation marks)	Judgement
Random sequence generation	"Eligible participants were randomized using an internet-based system with allocation concealment…Randomization was stratified by site, sex, and age, and the allocation was generated by a minimization algorithm." The method for sequence generation was judged appropriate.	Low
Allocation concealment	As above, allocation concealment was confirmed.	Low
Blinding of participants and personnel	"In this open-label, three-arm, adaptive, randomized controlled trial…" No blinding. The participants' and personnel's performance could have been biased due to their knowledge of the assigned treatment.	Unclear

[3] Study was reviewed by author fluent in the language of publication (simple mandarin)

Blinding of outcome assessors	"Tracheal intubation was performed when clinically indicated, based on the judgement of the treating clinician." Although blinding was not conducted, the administration/decision of intubation was based on participant's signs and symptoms and clinical judgement.	Low
Incomplete outcome data -mortality	"The primary outcome was a composite outcome of tracheal intubation or mortality within 30-days of randomization… The primary and secondary analyses were performed for the intention-to-treat (ITT) population…Primary outcome data were available for 99.0 % (1259/1272) of participants." The attrition was trivial, which was less likely to significantly influence the estimate of the effect size.	Low
Incomplete outcome data- IMV	As above, the attrition was trivial and outcome, intubation, was less likely to significantly influence the estimate of the effect size	Low
Selective outcome reporting	Trial protocol was posted online (statistical_analysis_plan_of_the_recovery-rs_trial_formal_v1.0_clean.pdf (warwick.ac.uk).The reported outcomes in the publication appear to match what have been pre-planned in the statistical analysis plan.	Low

Outcome tables: Mortality

Table B3: HFNO versus STANDARD OXYGEN

REF	N	OUTCOME	ARM 1	SOT n	SOT OUTCOME n	ARM 2	HFNO n	HFNO OUTCOME n	AGGREGATE DATA from PAPER
TENG ET AL. 2021	22	CURED AND DISCHARGED	STANDARD OXYGEN THERAPY	10	10 (CALC 0 DEATHS)	HFNO	12	12 (CALC 0 DEATHS)	"All patients in this study were cured and discharged."
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	MORTALITY AT 30 D	STANDARD OXYGEN	370	74	HFNO	415	78	BASED ON PRE-PRINT, HFNO versus Conventional Oxygen Therapy, UNADJUSTED OR = 0.93 (0.65-1.32) / ADJUSTED OR = 0.96 (0.64 - 1.45)

Table B4: CPAP versus STANDARD OXYGEN

REF	N	OUTCOME	ARM 1	SOT n	SOT OUTCOME n	ARM 2	NIV n	NIV OUTCOME n	AGGREGATE DATA from PAPER
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	MORTALITY AT 30 D	STANDARD OXYGEN	359	69	CPAP	378	63	BASED ON PRE-PRINT, CPAP VERSUS COT - UNADJUSTED OR = 0.84 (0.58 -1.23), ADJUSTED OR = 0.91 (0.59 -1.39)

Table B5: HELMET NIV versus HFNO

REF	N	OUTCOME	ARM 1	HFNO n	HFNO OUTCOME n	ARM 2	NIV n	NIV OUTCOME n	AGGREGATE DATA from PAPER
GREICO et al. 2021, HENIVOT trial NCT04502576	110	MORTALITY 28 D	HFNO	55	10	HELMET NIV	55	8	ABSOLUTE DIFFERENCE -3 (-17 TO 11), ODDS RATIO 0.78 (0.28 TO 2.16); P=0.80

GREICO et al. 2021, HENIVOT trial NCT04502576	110	MORTALITY 60 D	HFNO	55	12	HELMET NIV	55	13	ABSOLUTE DIFFERENCE 2 (-13 TO 18), ODDS RATIO 1.14 (0.46 TO 2.78) P = 0.82
GREICO et al. 2021, HENIVOT trial NCT04502576	110	MORTALITY 90 D	HFNO	55	PLANNED BUT NOT REPORTED	HELMET NIV	55	PLANNED BUT NOT REPORTED	PLANNED BUT NOT REPORTED

Table B6: CPAP versus HFNO

REF	N	OUTCOME	ARM 1	HFNO n	HFNO OUTCOME n	ARM 2	CPAP n	CPAP OUTCOME n	AGGREGATE DATA from PAPER
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	MORTALITY AT 30 D	HFNO	415	**78**	CPAP	378	**63**	BASED ON PRE-PRINT. NOT A COMPARISON MADE IN THE STUDY, CALCULATED CRUDE OR = 0.86 [0.60, 1.25], ITC OR 0.948 [0.524-1.714]

Outcome tables: IMV

Table B7: HFNO versus STANDARD OXYGEN

REF	N	OUTCOME	ARM 1	SOT n	SOT OUTCOME n	ARM 2	HFNO n	HFNO OUTCOME n	AGGREGATE DATA from PAPER
Li et al. 2020	72	MECHANICAL VENTILATION (12 H)	ROUTINE OXYGEN MASK INHALATION	35	6	HFNO	37	1	NR
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	INTUBATION WITHIN 30 D	CONVENTIONAL OXYGEN THERAPY	368	153	HFNO	414	170	BASED ON PRE-PRINT ONLY, **HFNO** versus Conventional Oxygen Therapy, ODDS RATIO UNADJUSTED 0.98 (0.74- 1.30) / ADJUSTED 0.96 (0.70 - 1.31)

Table B8: CPAP versus STANDARD OXYGEN

REF	N	OUTCOME	ARM 1	SOT n	SOT OUTCOME n	ARM 2	NIV n	NIV OUTCOME n	AGGREGATE DATA from PAPER
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	INTUBATION WITHIN 30 D	STANDARD OXYGEN	356	147	CPAP	377	126	BASED ON PRE-PRINT ONLY, CPAP VERSUS COT, UNADJUSTED OR = 0.71 (0.53- 0.96)/ ADJUSTED OR = 0.66 (0.47- 0.93)

Table B9: HELMET NIV versus HFNO

REF	N	OUTCOME	ARM 1	HFNO n	HFNO OUTCOME n	ARM 2	NIV n	NIV OUTCOME n	AGGREGATE DATA from PAPER
GREICO et al. 2021, HENIVOT trial NCT04502576	110	INTUBATION WITHIN 28D FROM ENROLLMENT (After adjudication of intubation criteria by external experts)	HFNO	55	28	HELMET NIV	55	15	Absolute difference HELMET V. HFNO −23 (−39 to −5) Odds ratio (95% CI) 0.37 (0.17 to 0.82), P =0.02 The rate of endotracheal intubation was significantly lower in the helmet group than in the HFNO group (30% vs 51%; difference, −21% [95% CI, −38%to −3%]; P = .03)

Table B10: CPAP versus HFNO

REF	N	OUTCOME	ARM 1	HFNO n	HFNO OUTCOME n	ARM 2	CPAP n	CPAP OUTCOME n	AGGREGATE DATA from PAPER
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	INTUBATION WITHIN 30 D	HFNO	414	170	CPAP	377	126	**COMPARISON WAS NOT MADE IN THE PAPER.** BASED ON PRE-PRINT ONLY, HFNO versus Conventional Oxygen Therapy, CALCULATED CRUDE ODDS

									RATIO UNADJUSTED 0.98 (0.74- 1.30) / ADJUSTED 0.96 (0.70 - 1.31), ITC OR 0.688 (0.433-1.093)

Outcome tables: Hospital and ICU LOS

Table B11: HFNO versus STANDARD OXYGEN

REF	N	OUTCOME	ARM 1	SOT MEAN	SOT SD	ARM 2	HFNO MEAN	HFNO SD	AGGREGATE DATA from PAPER
HOSPITAL LOS									
TENG ET AL 2021	22	TOTAL LENGTH OF HOSPITALIZATION, D	CONVENTIONAL OXYGEN THERAPY	16.6	2.54	HFNO	14.67	1.97	P= 0.058
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	HOSPITAL LOS, D	STANDARD OXYGEN	17.1	18	HFNO	18.3	20	MEAN DIFFERENCE FOR HFNO VERSUS COT UNADJUSTED = -1.25 (-1.46, 3.97) ADJUSTED OR 0.70 (-1.93, 3.34)
ICU LOS									
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	CRITICAL CARE LOS, D	STANDARD OXYGEN	9.5	14.1	HFNO	10.5	15.6	MEAN DIFFERENCE FOR HFNO VERSUS COT UNADJUSTED = 1.01 (-1.11, 3.14) ADJUSTED = 0.69 (-1.37, 2.75)
TENG ET AL 2021	22	LENGTH OF ICU STAY, D	CONVENTIONAL OXYGEN THERAPY	4.9	1	HFNO	4	0.74	P = .024

Table B12: CPAP versus STANDARD OXYGEN

REF	N	OUTCOME	ARM 1	SOT MEAN	SOT SD	ARM 2	MEAN NIV	NIV SD	AGGREGATE DATA from PAPER

HOSPITAL LOS									
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	HOSPITAL LOS, D	STANDARD OXYGEN	17.3	**18.1**	CPAP	16.4	**17.5**	MEAN DIFFERENCE FOR CPAP VERSUS COT UNADJUSTED = -0.96 (-3.59, 1.67) / ADJUSTED = -0.97 (-3.65, 1.71)
ICU LOS									
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	CRITICAL CARE LOS, D	STANDARD OXYGEN	9.6	**13.6**	CPAP	9.5	**15.6**	MEAN DIFFERENCE FOR CPAP VERSUS COT UNADJUSTED = -0.08 (-2.23, 2.07) / ADJUSTED = -0.33 (-2.44, 1.78)

Table B13: HELMET NIV versus HFNO

REF	N	OUTCOME	ARM 1	HFNO MEAN	HFNO SD	ARM 2	HELMET NIV MEAN	HELMET NIV SD	AGGREGATE DATA from PAPER
HOSPITAL LOS									
GREICO et al. 2021, HENIVOT trial NCT04502576	110	HOSPITAL LOS, D	HFNO	MEDIAN 22	IQR 13 TO 44	HELMET NIV	MEDIAN 21	IQR 14 TO 30	absolute Mean difference (DIFFERENCE IN MEANS) HELMET V. HFNO (95% CI) −6 (−14 to 1) Odds ratio (95% CI) Not reported, p=0.47

ICU LOS									
GREICO et al. 2021, HENIVOT trial NCT04502576	110	ICU LOS, D	HFNO	MEDIAN 10	IQR 5 TO 23	HELMET NIV	MEDIAN 9	IQR 4 TO 17	absolute Mean difference (DIFFERENCE IN MEANS) HELMET V. HFNO (95% CI) −6 (−13 to 1) Odds ratio (95% CI) Not reported, p=0.22

Table B14: CPAP versus HFNO

REF	N	OUTCOME	ARM 1	HFNO MEAN	HFNO SD	ARM 2	CPAP MEAN	CPAP SD	AGGREGATE DATA from PAPER
HOSPITAL LOS									
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	HOSPITAL LOS, D	HFNO	MEAN 18.3	SD 20.0	CPAP	MEAN 16.4	SD 17.5	BASED ON PRE-PRINT. NOTE THAT THIS COMPARISON WAS NOT MADE IN THE PAPER. ITC MD -1.67 (-5.428, 2.088)
ICU LOS									
PERKINS ET AL, 2021 (RECOVERY-RS)	1272	CRITICAL CARE LOS, D	HFNO	MEAN 10.5	SD 15.6	CPAP	MEAN 9.5	SD 15.6	BASED ON PRE-PRINT. NOTE THAT THIS COMPARISON WAS NOT MADE IN THE PAPER. ITC MD -1.02 (-3.969, 1.929)

Table B15: Indirect data calculations for CPAP vs HFNO exploratory analyses (RECOVERY-RS)

OUTCOME	RCT data reported		INDIRECT TREATMENT COMPARISON
	HFNO versus SOT	CPAP versus SOT	CPAP versus HFNO (ITC DATA)
MORTALITY AT 30 D	ADJUSTED OR = 0.96 (0.64 - 1.45)	ADJUSTED OR = 0.91 (0.59 -1.39)	RR 0.948 (0.524-1.714)
IMV AT 30D	ADJUSTED OR 0.96 (0.70 - 1.31)	ADJUSTED OR = 0.66 (0.47- 0.93)	RR 0.688 (0.433-1.093)
HOSPITAL LOS, D	MD 0.70 (-1.93, 3.34)	MD -0.97 (-3.65, 1.71)	MD -1.67 (-5.428, 2.088)
ICU LOS, D	MD 0.69 (-1.37, 2.75)	MD -0.33 (-2.44, 1.78)	MD -1.02 (-3.969, 1.929)

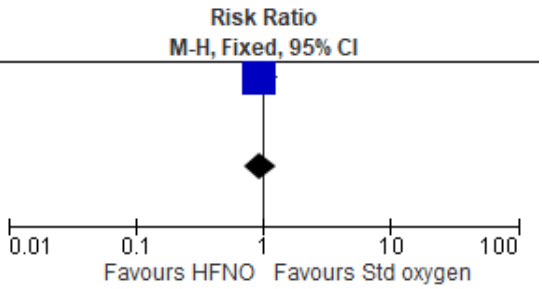
Forest plots: Direct PICO

HFNO versus SOT

30 d Mortality

Study or Subgroup	HFNO Events	HFNO Total	Std Oxygen Events	Std Oxygen Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RECOVERY-RS 2021	78	415	74	370	100.0%	0.94 [0.71, 1.25]
Teng 2021	0	12	0	10		Not estimable
Total (95% CI)		**427**		**380**	**100.0%**	**0.94 [0.71, 1.25]**
Total events	78		74			

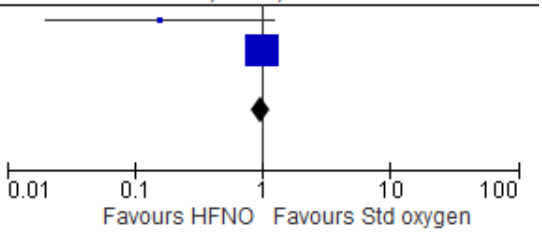
Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)



IMV

Study or Subgroup	HFNO Events	HFNO Total	Std Oxygen Events	Std Oxygen Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Li 2020	1	37	6	35	3.7%	0.16 [0.02, 1.24]
RECOVERY-RS 2021	170	414	153	368	96.3%	0.99 [0.84, 1.17]
Total (95% CI)		**451**		**403**	**100.0%**	**0.96 [0.81, 1.13]**
Total events	171		159			

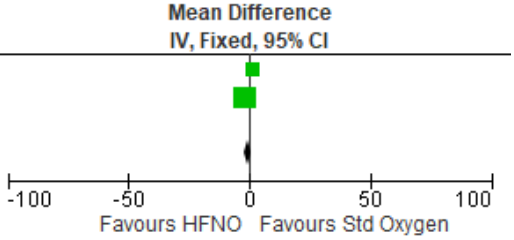
Heterogeneity: Chi² = 3.06, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 0.51 (P = 0.61)



Hospital LOS

Study or Subgroup	HFNO Mean	HFNO SD	HFNO Total	Std Oxygen Mean	Std Oxygen SD	Std Oxygen Total	Weight	Mean Difference IV, Fixed, 95% CI
RECOVERY-RS 2021	18.3	20	414	17.1	18	368	34.4%	1.20 [-1.46, 3.86]
Teng 2021	14.67	1.97	12	16.6	2.54	10	65.6%	-1.93 [-3.86, -0.00]
Total (95% CI)			**426**			**378**	**100.0%**	**-0.85 [-2.42, 0.71]**

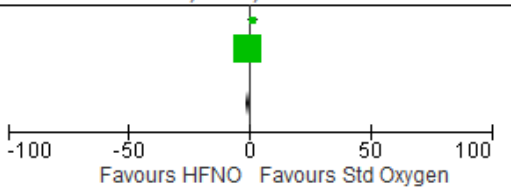
Heterogeneity: Chi² = 3.48, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 1.07 (P = 0.28)



ICU LOS

Study or Subgroup	HFNO Mean	HFNO SD	HFNO Total	Std Oxygen Mean	Std Oxygen SD	Std Oxygen Total	Weight	Mean Difference IV, Fixed, 95% CI
RECOVERY-RS 2021	10.5	15.6	414	9.5	14.1	368	11.4%	1.00 [-1.08, 3.08]
Teng 2021	4	0.74	12	4.9	1	10	88.6%	-0.90 [-1.65, -0.15]
Total (95% CI)			**426**			**378**	**100.0%**	**-0.68 [-1.39, 0.02]**

Heterogeneity: Chi² = 2.83, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 1.90 (P = 0.06)

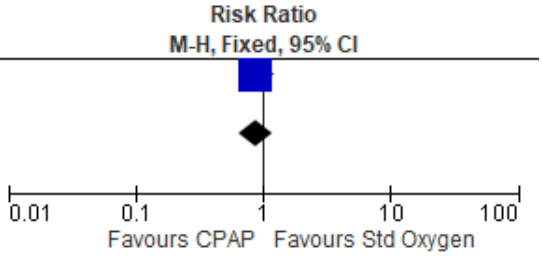


CPAP versus SOT

30d mortality

Study or Subgroup	CPAP Events	CPAP Total	Std Oxygen Events	Std Oxygen Total	Weight	Risk Ratio M-H, Fixed, 95% CI
RECOVERY-RS 2021	63	378	69	359	100.0%	0.87 [0.64, 1.18]
Total (95% CI)		**378**		**359**	**100.0%**	**0.87 [0.64, 1.18]**
Total events	63		69			

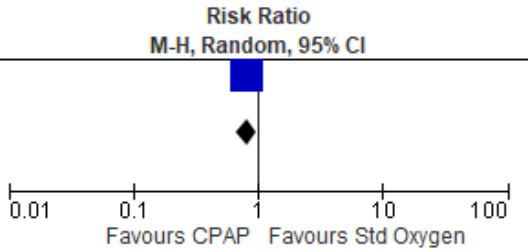
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



IMV

Study or Subgroup	CPAP Events	CPAP Total	Std Oxygen Events	Std Oxygen Total	Weight	Risk Ratio M-H, Random, 95% CI
RECOVERY-RS 2021	126	377	147	356	100.0%	0.81 [0.67, 0.98]
Total (95% CI)		**377**		**356**	**100.0%**	**0.81 [0.67, 0.98]**
Total events	126		147			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.20 (P = 0.03)



Appendix C: Additional tables and figures - Rapid evidence review for the indirect PICO

Summary of RCT study and participant characteristics: indirect PICO

Table C1: Indirect PICO RCT study characteristics

Study	N	Intervention	Comparator 1	Comparator 2	Outcomes reported				Study funding	Overall ROB for all-cause mortality*	Overall ROB for IMV*
					Mortality	IMV	Hospital LOS	ICU LOS			
Andino et al. 2020[5]	46	HFNC (n=24)	Standard oxygen (n=22)	NA	Y	Y	Y	Y	Spanish Ministry of Health, Social Services, and Equality	Low	High
Antonelli et al, 2000[6]	40	Face mask noninvasive ventilation (n = 20)	Standard oxygen (n = 20)	NA	Y	Y	Y	Y	Undisclosed	Low	Unclear
Azevedo et al., 2015[7]	67	High-flow nasal oxygen (n = 14)	Face mask noninvasive ventilation (n = 16)	NA	N	Y	N	N	Undisclosed	Unclear, **abstract only	Unclear, **abstract only
Azoulay et al, 2018[8]	776	High-flow nasal oxygen (n = 388)	Standard oxygen (n = 388)	NA	Y	Y	Y	Y	French Ministry of Health	Low	Unclear
Brambilla et al, 2014[9]	81	Helmet CPAP (n=40)	Standard oxygen (n = 41)	NA	Y	Y	Y	N	IRCCS Fondazione Ca'Granda, Ospedale Maggiore Policlinico, Milan	Unclear	High

Study	N	Intervention	Comparator 1	Comparator 2	Outcomes reported				Study funding	Overall ROB for all-cause mortality*	Overall ROB for IMV*
					Mortality	IMV	Hospital LOS	ICU LOS			
Confalonieri et al, 1999[10]	56	Face mask noninvasive ventilation (n = 28)	Standard oxygen (n = 28)	NA	Y	Y	Y	Y	Undisclosed	Low	Unclear
Cosentini et al, 2010b[11]	47	Helmet CPAP(n = 20)	Standard oxygen (n = 27)	NA	Y	Y	N	N	Undisclosed	Low	Unclear
Delclaux et al, 2000[12]	123	Face mask CPAP (n = 62)	Standard oxygen (n = 61)	NA	Y	Y	Y	Y	Vital Signs Inc	Low	Unclear
Ferrer et al, 2003[13]	105	Face mask noninvasive ventilation (n = 51)	Standard oxygen (n = 54)	NA	Y	Y	Y	Y	Red GIRA, Red Respira, and Carburos Metalicos SA	Low	Unclear
Frat et al, 2015[14,27]	310	HFNO (n=106)	Face mask noninvasive ventilation (n = 110)	Standard oxygen (n = 94)	Y	Y	N	Y	French Ministry of Health	Low	Unclear
Hernandez et al, 2010[16]	50	Face mask noninvasive ventilation (n = 25)	Standard oxygen (n = 25)	NA	Y	Y	Y	Y	Consejería de Sanidad de Castilla	Low	Unclear
He et al, 2019[15]	200	Face mask noninvasive ventilation (n = 102)	Standard oxygen (n = 98)	NA	Y	Y	Y	Y	National Natural Science Foundation of China	High	High
Hilbert et al, 2001[17]	52	Face mask noninvasive ventilation (n = 26)	Standard oxygen (n = 26)	NA	Y	Y	N	Y	Undisclosed	Low	Unclear

Study	N	Intervention	Comparator 1	Comparator 2	Outcomes reported				Study funding	Overall ROB for all-cause mortality*	Overall ROB for IMV*
					Mortality	IMV	Hospital LOS	ICU LOS			
Jones et al, 2016[18]	303	HFNO (n=165)	Standard oxygen (n = 138)	NA	Y	Y	Y	N	Greenlane Research and Education Fund	High	High
Lemiale et al, 2015[20]	374	Face mask noninvasive ventilation (n = 191)	Standard oxygen (n = 183)	NA	Y	Y	Y	Y	Legs Poix (Chancellerie des Universités de Paris) and OUTCOMEREA Study Group	Low	Unclear
Lemiale et al, 2015[2h][19]	100	HFNO (n=52)	Standard oxygen (n = 48)	NA	N	Y	N	N	Fisher & Paykel	High	High
Patel et al, 2016[21,28]	83	Helmet NIV (n=44)	Face mask NIV (n = 39)	NA	Y	Y	Y	Y	National Institutes of Health/National Heart, Lung, and Blood Institute	Low	Unclear
Shebl et al. 2018[22]	70	NPPV (n=36)	HFNC (n=34)	NA	Y	Y	N	N	Nil.	Unclear	Unclear/Probably High
Squadrone 2010[23]	40	Helmet CPAP (n = 20)	Standard oxygen (n = 20)	NA	Y	Y	N	N	Regione Piemonte (CEP AN RAN 07) and Ministero dell'Università (PRIN RANI 07)	Low	Unclear

Study	N	Intervention	Comparator 1	Comparator 2	Outcomes reported				Study funding	Overall ROB for all-cause mortality*	Overall ROB for IMV*
					Mortality	IMV	Hospital LOS	ICU LOS			
Wermke et al., 2012[24]	86	Face mask noninvasive ventilation (n = 42)	Standard oxygen (n = 44)	NA	Y	Y	N	N	Undisclosed	Unclear	High
Wysocki et al., 1995[25]	41	Face mask noninvasive ventilation (n = 21)	Standard oxygen (n = 20)	NA	Y	Y	N	Y	Undisclosed	Low	Unclear
Zhan et al., 2012[26]	40	Face mask noninvasive ventilation (n = 21)	Standard oxygen (n = 19)	NA	Y	Y	Y	Y	Beijing Municipal Science and Technology Commission Program	Low	Unclear

*Risk of bias assessment by outcome extracted from original systematic review

Table C2: Indirect PICO RCT participant characteristics Indirect PICO RCT study characteristics

Study	N	Main baseline risk factor	Main exposure	Comparator 1	Comparator 2	Age, mean, y	PaO_2/FiO_2 ratio	Respiratory rate, /min
Andino et al. l. 2020[5]	46	AHRF (pneumonia [62%])	HFNC (n=24)	Standard oxygen (n=22)	NA	HFNC: 58 (19) COT: 61 (11)	HFNC: 96 (29) COT: 95 (37)	NR
Antonelli et al, 2000[6]	40	Mixed ARF [immunocompromised (100%)]	Face mask noninvasive ventilation (n = 20)	Standard oxygen (n = 20)	NA	45	129	38
Azevedo et al, 2015[7]	67	CAP (CHF [43%])	High-flow nasal oxygen (n = 14)	Face mask noninvasive ventilation (n = 16)	NA	median 64	NR	NR
Azoulay et al, 2018[8]	776	CAP [immunocompromised (100%)]	High-flow nasal oxygen (n = 388)	Standard oxygen (n = 388)	NA	median 64	132	33
Brambilla et al, 2014[9]	81	CAP [immunocompromised (32%)]	Helmet CPAP (n=40)	Standard oxygen (n = 41)	NA	67	141	34
Confalonieri et al, 1999[10]	56	CAP	Face mask noninvasive ventilation (n = 28)	Standard oxygen (n = 28)	NA	64	175	37
Cosentini et al, 2010b[11]	47	CAP	Helmet CPAP (n = 20)	Standard oxygen (n = 27)	NA	69	248	27

Study	N	Main baseline risk factor	Main exposure	Comparator 1	Comparator 2	Age, mean, y	PaO_2/FiO_2 ratio	Respiratory rate, /min
Delclaux et al., 2000[12]	123	CAP	Face mask CPAP (n = 62)	Standard oxygen (n = 61)	NA	Median 58	144	33
Ferrer et al., 2003[13]	105	CAP (immunocompromised [20%]; CHF [28%])	Face mask noninvasive ventilation (n = 51)	Standard oxygen (n = 54)	NA	62	103	37
Frat et al, 2015[14,27]	310	CAP [immunocompromised (26.5%)]	HFNO (n=106)	Face mask noninvasive ventilation (n = 110)	Standard oxygen (n = 94)	60	155	33
Hernandez et al, 2010[16]	50	Chest trauma	Face mask noninvasive ventilation (n = 25)	Standard oxygen (n = 25)	NA	43	109	NR
He et al, 2019[15]	200	CAP	Face mask noninvasive ventilation (n = 102)	Standard oxygen (n = 98)	NA	55	231	25
Hilbert et al, 2001[17]	52	CAP [immunocompromised (100%)]	Face mask noninvasive ventilation (n = 26)	Standard oxygen (n = 26)	NA	49	139	36
Jones et al., 2016[18]	303	Mixed ARF (COPD [23.9%]; CHF [12.3%])	HFNO (n=165)	Standard oxygen (n = 138)	NA	73	NR	33
Lemiale et al, 2015[20]	374	Pneumonia [immunocompromised (100%)]	Face mask noninvasive ventilation (n = 191)	Standard oxygen (n = 183)	NA	median 63	142	26

Study	N	Main baseline risk factor	Main exposure	Comparator 1	Comparator 2	Age, mean, y	PaO_2/FiO_2 ratio	Respiratory rate, /min
Lemiale et al, 2015[2h][19]	100	Mixed ARF [immunocompromised (100%)]	HFNO (n=52)	Standard oxygen (n = 48)	NA	median 62	114	27
Patel et al, 2016[21,28]	83	CAP [immunocompromised (100%)]	Helmet NIV (n=44)	Face mask NIV (n = 39)	NA	median 60	131	28
Shebl et al. 2018[22]	70	AHRF (interstitial lung disease [100%])	NPPV (n=36)	HFNC (n=34)	NA	NPPV: 61 (12) HFNC: 61 (12)	NPPV: 166 (42) HFNC: 178 (55)	NPPV: 30.1 (5.2) HFNC: 31.3 (4.8)
Squadrone 2010[23]	40	Mixed ARF (hematologic malignancies [100%])	Helmet CPAP (n = 20)	Standard oxygen (n = 20)	NA	49	269	30
Wermke et al., 2012[24]	86	CAP (immunocompromised [100%])	Face mask noninvasive ventilation (n = 42)	Standard oxygen (n = 44)	NA	median 52	270	NR
Wysocki et al., 1995[25]	41	CAP (CHF [30%])	Face mask noninvasive ventilation (n = 21)	Standard oxygen (n = 20)	NA	63	207	35
Zhan et al., 2012[26]	40	ALI (immunocompromised [30%])	Face mask noninvasive ventilation (n = 21)	Standard oxygen (n = 19)	NA	46	230	20

Outcome tables: Mortality

Table C3: HFNO versus STANDARD OXYGEN (3 RCTs) - MORTALITY AT END OF STUDY

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	HFNO OUTCOME	HFNO n	AGGREGATE DATA from PAPER
Frat et al, 2015 (FLORALI)	313	90 DAY MORTALITY (Whole population)	STANDARD OXYGEN THERAPY	22	94	HFNO	13	106	UNADJUSTED HR (95% CI) 2.01 (1.01–3.99) ADJUSTED HR 2.36 (1.18–4.70) Standard Oxygen vs. High-Flow Oxygen P-VALUES ARE FOR THE 3-GROUP COMPARISON
Jones et al, 2016	322	90 DAY MORTALITY	STANDARD OXYGEN THERAPY	24	150	HFNO	35	172	NR
Andino et al. 2020	46	MORTALITY	CONVENTIONAL OXYGEN THERAPY	18% (calc = 4)	22	HFNC	25% (calc = 6)	24	NR
Azoulay et al. 2018	776	28 D MORTALITY	STANDARD OXYGEN THERAPY	140	388	HFNO	138	388	MD −0.5 (−7.3 to 6.3) HR, 0.98 (0.77 to 1.24) p=0.94

Table C12:HFNO versus STANDARD OXYGEN - MORTALITY 28d

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	HFNO OUTCOME	HFNO n	AGGREGATE DATA from PAPER
Azoulay et al. 2018	776	28 D MORTALITY	STANDARD OXYGEN THERAPY	140	388	HFNO	138	388	MD −0.5 (−7.3 to 6.3) HR, 0.98 (0.77 to 1.24) p=0.94

Table C4: HFNO versus STANDARD OXYGEN - MORTALITY 90d

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	HFNO OUTCOME	HFNO n	AGGREGATE DATA from PAPER
Frat et al., 2015 (FLORALI)	313	90 DAY MORTALITY (Whole population)	STANDARD OXYGEN THERAPY	22	94	HFNO	13	106	Standard Oxygen vs. High-Flow Oxygen Unadjusted analysis p=0.02 HR 2.01 (1.01–3.99) Adjusted analysis HR 2.36 (1.18–4.70)
Jones et al, 2016	322	90 DAY MORTALITY	STANDARD OXYGEN THERAPY	24	150	HFNO	35	172	NR

Table C5: HELMET CPAP versus STANDARD OXYGEN - HOSPITAL MORTALITY

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	Helmet CPAP OUTCOME	Helmet CPAP n	AGGREGATE DATA from PAPER
Brambilla et al, 2014 (HIGH)	81	IN-HOSPITAL MORTALITY	OXYGEN	7	41	CPAP HELMET	2	40	p=0.155
Cosentini et al, 2010b	47	*"MORTALITY DURING TREATMENT"*	OXYGEN	0	27	CPAP HELMET	0	20	No patient ..died during treatment.
Squadrone et al, 2010	40	HOSPITAL MORTALITY	STD OXYGEN	15	20	CPAP HELMET	3	20	Kaplan Meier, Reduction of RR for death was 0.20 (95% confidence interval: 0.07–0.58;p=0.0004), and the NNT was 1.7

Table C6: NIV FACEMASK versus STANDARD OXYGEN - BEST AVAILABLE MORTALITY

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	Facemask NIV OUTCOME	Facemask NIV n	AGGREGATE DATA from PAPER
Antonelli et al, 2000	40	HOSPITAL DEATH	OXYGEN	11	20	FULL FACEMASK NIV	7	20	P=0.17

Confalonieri et al, 1999	56	HOSPITAL DEATH (whole population)	OXYGEN	6	28	FULL FACEMASK NPPV	7	28	"ns"
Confalonieri et al, 1999	56	2 MONTH SURVIVAL (CALC = 60 DAY DEATHS)(whole population)	OXYGEN	18 (CALC = 10 DIED)	28	FULL FACEMASK NPPV	21 (CALC =7 DIED)	28	"ns"
Ferrer et al, 2003	105	MORTALITY 90 D	OXYGEN FROM HIGH CONCENTRATION SOURCES	21	54	BIPAP (FACE MASK OR NASAL IF NOT TOLERATED)	10	51	NR
Frat et al, 2015 (FLORALI)	313	90 DAY MORTALITY (Whole population)	STANDARD OXYGEN THERAPY	22	96	FACEMASK NIV	31	110	USE ITC Comparison not made, only crude data available
Frat et al. 2016 (SUBGROUP)	82	90 DAY MORTALITY (Immunocompromised)	STANDARD OXYGEN THERAPY	8	30	FACEMASK NIV	12	26	USE ITC Comparison not made, only crude data available
Hernandez et al, 2010	50	HOSPITAL MORTALITY	STD OXYGEN	1	25	BIPAP FULL FACEMASK OR FACEMASK BASED ON INJURIES AND TOLERANCE	1	25	P=1.0
He et al, 2019 (ENIVA)	204	DEATH IN HOSPITAL	CONVENTIONAL OXYGEN THERAPY	7	99	ORONASAL MASK BIPAP	7	105	P=0.95
Hilbert et al, 2001	52	DEATH IN HOSPITAL	SUPPLEMENTAL OXYGEN	21	26	INTERMITTANT FULL FACEMASK NIV AND SUPPLEMENTAL OXYGEN	13	26	RR=0.62 (0.40–0.95);P=0.02

Lemiale et al, 2015	374	MORTALITY, 28D	STANDARD OXYGEN	50	183	FACEMASK NIV	46	191	ODDS RATIO 0.84 (0.53-1.34) ABSOLUTE DIFFERENCE = −3.2 (−12.1 to 5.6); P=0.47
Lemiale et al, 2015	374	MORTALITY, 6 MONTHS	STANDARD OXYGEN	82	183	FACEMASK NIV	72	191	ABSOLUTE DIFFERENCE −5.7 (−16.4 to 3.9);P=0.23
Wermke et al, 2012	86	100d SURVIVAL	OXYGEN	68% (calc 29.92)	44	OXYGEN PLUS INTERMITTANT FULL FACEMASK NIV	61% (calc 25.62)	42	*17 pts failing on arm A crossed over to arm B, which may impact outcomes after ICU admission.
Wysocki et al., 1995	41	ICU DEATH	CONVENTIONAL OXYGEN	10	20	CONVENTIONAL OXYGEN PLUS FULL FACE MASK NIPSV (PRESSURE SUPPORT VENTILATION)	7	21	P=0.46
Zhan et al, 2012	40	HOSPITAL DEATH	HIGH CONCENTRATION CONVENTIONAL OXYGEN THERAPY (STANDARD OXYGEN)	5	19	NIPPV - FACEMASK BIPAP	1	21	p=0.09

Table C7: NIV FACEMASK versus STANDARD OXYGEN - 30 d MORTALITY

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	Facemask NIV OUTCOME	Facemask NIV n	AGGREGATE DATA from PAPER
Lemiale et al, 2015	374	MORTALITY, 28D	STANDARD OXYGEN	50	183	FACEMASK NIV	46	191	ODDS RATIO 0.84 (0.53-1.34) ABSOLUTE DIFFERENCE = −3.2 (−12.1 to 5.6); P=0.47

Table C8: NIV FACEMASK versus STANDARD OXYGEN - 60 d MORTALITY

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	Facemask NIV OUTCOME	Facemask NIV n	AGGREGATE DATA from PAPER
Confalonieri et al, 1999	56	2 MONTH SURVIVAL (CALC = 60 DAY DEATHS)(whole population)	OXYGEN	18 (CALC = 10 DIED)	28	FULL FACEMASK NPPV	21 (CALC =7 DIED)	28	"ns"

Table C9: NIV FACEMASK versus STANDARD OXYGEN - 90 d MORTALITY

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	Facemask NIV OUTCOME	Facemask NIV n	AGGREGATE DATA from PAPER
Wermke et al, 2012	86	100d SURVIVAL	OXYGEN	68% (calc 29.92)	44	OXYGEN PLUS INTERMITTANT FULL FACEMASK NIV	61% (calc 25.62)	42	*17 pts failing on arm A crossed over to arm B, which may impact outcomes after ICU admission.
Ferrer et al, 2003	105	MORTALITY 90 D	OXYGEN FROM HIGH CONCENTRATION SOURCES	21	54	BIPAP (FACE MASK OR NASAL IF NOT TOLERATED)	10	51	NR
Frat et al, 2015 (FLORALI)	313	90 DAY MORTALITY (Whole population)	STANDARD OXYGEN THERAPY	22	94	FACEMASK NIV	31	110	

Table C10: FACEMASK CPAP versus STANDARD OXYGEN - HOSPITAL MORTALITY

RCT	N	OUTCOME	ARM 1	SOT OUTCOME	SOT n	ARM 2	Facemask CPAP OUTCOME	Facemask CPAP n	AGGREGATE DATA from PAPER
Delclaux et al, 2000	123	HOSPITAL MORTALITY	OXYGEN	15	61	OXYGEN AND FULL FACEMASK CPAP	13	62	p=0.89

Table C11: NIV - FACEMASK versus HFNO - ANY MORTALITY

RCT	N	OUTCOME	ARM 1	HFNO OUTCOME	HFNO n	ARM 2	Facemask NIV OUTCOME	Facemask NIV n	AGGREGATE/OTHER DATA from PAPER
Frat et al, 2015 (FLORALI)	313	90 DAY MORTALITY (Whole population)	HFNO	13	106	FACEMASK NIV	31	110	unadjusted HR 2.50 (1.31–4.78), adjusted HR 2.33 (1.22–4.47)
Shebl et al. 2018	70	IN-HOSPITAL MORTALITY	HFNOT	9	34	NIV - BIPAP VISION WITH Continuous positive airway pressure mode was initiated	11	36	P=0.71

Table C12: NIV - FACEMASK versus HFNO - 90 d MORTALITY

RCT	N	OUTCOME	ARM 1	HFNO OUTCOME	HFNO n	ARM 2	Facemask NIV OUTCOME	Facemask NIV n	AGGREGATE/OTHER DATA from PAPER
Frat et al, 2015 (FLORALI)	313	90 DAY MORTALITY (Whole population)	HFNO	13	106	FACEMASK NIV	31	110	unadjusted HR 2.50 (1.31–4.78), adjusted HR 2.33 (1.22–4.47)

Table C13: NIV - HELMET versus NIV - FACEMASK - 90 D MORTALITY

RCT	N	OUTCOME	ARM 1	Facemask NIV OUTCOME	Facemask NIV n	ARM 2	Helmet NIV OUTCOME	Helmet NIV n	AGGREGATE/OTHER DATA from PAPER
Patel et al, 2016	83	90D MORTALITY	FACEMASK NIV AND MORE FACEMASK NIV	22	39	FACEMASK NIV THEN HELMET NIV	15	44	Absolute Difference (95% CI)−22.3 (−43.3 to −1.4); P=.02 unadjusted HR for death at 90 days was 0.47 (95%CI, 0.24 to 0.91 days; P = .03) in the helmet group

Table C14: NIV - HELMET versus NIV - FACEMASK - 1 y MORTALITY

RCT	N	OUTCOME	ARM 1	Facemask NIV OUTCOME	Facemask NIV n	ARM 2	Helmet NIV OUTCOME	Helmet NIV n	AGGREGATE/OTHER DATA from PAPER
Patel et al., 2016	Companion reports data PATEL 2018	1-year MORTALITY	FACEMASK NIV AND MORE FACEMASK NIV	27	39	FACEMASK NIV THEN HELMET NIV	19	44	p=0.007 The unadjusted HR for death at one year was 0.46 (95% confidence interval (CI) [0.25–0.82]; p=0.009) in the helmet NIV group. The risk of death at one year remained significantly lower in the helmet NIV group after adjustment for APACHE II score (HR 0.48 [0.26–0.86], p=0.01).

Outcome tables: IMV

Table C15: HFNO VERSUS SOT

RCT	N	OUTCOME	ARM 2	HFNO OUTCOME	HFNO n	ARM 1	SOT OUTCOME	SOT n	AGGREGATE DATA from PAPER
Frat et al, 2015 (FLORALI)	313	ENDOTRACHEAL INTUBATION AT DAY 28	HFNO	40	106	STANDARD OXYGEN THERAPY	44	94	OR 1.85 (0.84–4.09);
Jones et al, 2016	322	INTUBATED (Endotracheal)	HFNO	1	172	STANDARD OXYGEN THERAPY	3	150	p=0.33
Andino et all. 2020	46	Endotracheal intubation	HFNC	8	24	CONVENTIONAL OXYGEN THERAPY	14	22	intention to treat [$\chi 2$ = 4.2; p = 0.04, relative risk (RR): 0.5, 95% confidence interval (CI): 0.3–1.0) and in treatment analysis ($\chi 2$ = 4.7; p = 0.03; RR = 0.5; CI 95%: 0.3–0.9)
Lemiale et al, 2015 - 2hrs	100	Need for IMV (within 24 hours)	HFNO	1 more (calc 5)	52	STANDARD OXYGEN THERAPY	2 more (calc 4)	48	NR

Table C16: HELMET CPAP VERSUS SOT

RCT	N	OUTCOME	ARM 2	Helmet CPAP OUTCOME	Helmet CPAP HELMET n	ARM 1	SOT OUTCOME	SOT n	AGGREGATE/OTHER DATA from PAPER
Brambilla et al, 2014 (HIGH)	81	ENDOTRACHEAL INTUBATION	CPAP HELMET	2	40	OXYGEN	1	41	NR

Cosentini et al, 2010b	47	REQUIRED INTUBATION DURING TRT	HELMET CPAP	0	20	OXYGEN	0	27	NR
Squadrone et al, 2010	40	Intubation and invasive ventilation at ICU entry	HELMET	2	20	STD OXYGEN	8	20	RR 0.5 (0.29–0.85) 0.03, P=0.03

Table C17: FACEMASK CPAP VERSUS SOT

RCT	N	OUTCOME	ARM 2	Facemask CPAP OUTCOME	Facemask CPAP HELMET n	ARM 1	SOT OUTCOME	SOT n	AGGREGATE/OTHER DATA from PAPER
Delclaux et al. 2000	123	Endotracheal intubation	FACEMASK CPAP	21	62	OXYGEN	24	61	p=0.53

Table C18: FACEMASK NIV VERSUS SOT

RCT	N	OUTCOME	ARM 2	FACEMASK NIV OUTCOME	FACEMASK NIV n	ARM 1	SOT OUTCOME	SOT n	AGGREGATE/OTHER DATA from PAPER
Antonelli et al, 2000	40	PTS REQUIRING INTUBATION	FULL FACEMASK NIV	4	20	OXYGEN	14	20	P=0.002
Confalonieri et al., 1999	56	Need for ETI and mechanical ventilation at any time during the study	FULL FACEMASK NPPV	6	28	OXYGEN	14	28	NR
Ferrer et al, 2003	105	Intubation rate	BIPAP (FACE MASK OR NASAL IF NOT TOLERATED)	13	51	OXYGEN FROM HIGH CONCENTRATION SOURCES	28	54	p=0.010
Frat et al, 2015 (FLORALI)	313	proportion of pts who required endotracheal intubation within	FACEMASK NIV	55	110	STANDARD OXYGEN THERAPY	44	94	Standard Oxygen vs. High-Flow Oxygen OR 1.45 (0.83–2.55)

		28 days after randomization.							
Hernandez et al, 2010	50	INTUBATION RATE	HFNO THEN BIPAP FULL FACEMASK OR FACEMASK BASED ON INJURIES AND TOLERANCE)	3	25	STANDARD OXYGEN	10	25	P=0.02
He et al, 2019 (ENIVA)	204	INTUBATION	ORONASAL MASK BIPAP	7	105	CONVENTIONAL OXYGEN THERAPY	9	99	P=0.71
Hilbert et al., 2001	52	Need for endotracheal intubation and mechanical ventilation at any time during the study	INTERMITTANT FULL FACEMASK NIV AND SUPPLEMENTAL OXYGEN	12	26	SUPPLEMENTAL OXYGEN	20	26	RR 0.60 (0.38–0.96); P=0.03
Lemiale et al, 2015	374	PATIENTS REQUIRING INTUBATION/NEED FOR INVASIVE MECHANICAL VENTILATION	FACEMASK NIV	73	191	STANDARD OXYGEN	82	183	absolute difference, −6.6 [95% CI, −16.6 to 3.4]; P = .20)
Wysocki et al., 1995	41	endotracheal intubation and mechanical ventilation	CONVENTIONAL OXYGEN PLUS FULL FACE MASK NIPSV (PRESSURE SUPPORT VENTILATION)	13	21	CONVENTIONAL OXYGEN	14	20	NR
Zhan et al, 2012	40	Intubation	NIPPV - FACEMASK BIPAP	1	21	(STANDARD OXYGEN)	4	19	p=0.04

Table C19: FACEMASK NIV VERSUS HFNO

RCT	N	OUTCOME	ARM 2	FACEMASK NIV OUTCOME	FACEMASK NIV n	ARM 1	HFNO OUTCOME	HFNO n	AGGREGATE/OTHER DATA from PAPER
Frat et al, 2015 (FLORALI)	313	ENDOTRACHEAL INTUBATION AT DAY 28	FACEMASK NIV	55	110	HFNO	40	106	OR 1.65 (0.96–2.84) FOR Noninvasive Ventilation vs. High-Flow Oxygen
Shebl et al. 2018	70	need for intubation within 28 days after admission to the ICU	NIV - BIPAP VISION WITH Continuous positive airway pressure mode was initiated	8	36	HFNOT	7	34	P=0.87
Azevedo et al, 2015 abstract only	35 (30 REPORTED)	INTUBATION	FACEMASK NIV	9	16 ANALYZED	HFNO	9	14 ANALYZED	P=0.72

Table C20: FACEMASK NIV VERSUS HELMET NIV

RCT	N	OUTCOME	ARM 2	Helmet NIV OUTCOME	Helmet NIV n	ARM 1	FACEMASK NIV OUTCOME	FACEMASK NIV n	AGGREGATE/OTHER DATA from PAPER
Patel et al., 2016	83	patients who underwent endotracheal intubation	FACEMASK NIV THEN HELMET NIV	8	44	FACEMASK NIV AND MORE FACEMASK NIV	24	39	Absolute Difference (95% CI) −43.3 (−62.4 to −24.3);P= <.001.In a competing risk analysis, the unadjusted subhazard ratio for the helmet group for the primary outcome of endotracheal intubation was 0.22 (95%CI, 0.11-0.47; P < .001).

Syntheses for hospital and ICU LOS

LOS data

Table C21: Hospital LOS syntheses

Comparison	Median and Mean (Metamedian[47])					
	K	EST	SE	I^2	LCI	UCI
HFNO VERSUS SOT	2	-1.17	1.02	33.59	-3.16	0.83
HELMET CPAP VERSUS SOT	1	0.50	2.17	NE	-3.75	4.75
FACEMASK CPAP VERSUS SOT	1	-2.00	7.91	NE	-17.50	13.50
FACEMASK NIV VERSUS SOT	6	-2.02	1.21	54.76	-4.39	0.35
FACEMASK NIV VERSUS HFNO	0					
NIV - HEMLET VERSUS NIV - FACEMASK	1	-5.10	2.18	NA	-9.38	-0.82

K=number of RCTs; est=absolute mean difference, in days; SE=standard error; NE=not estimable; LCL=lower 95% CI; UCI=upper 95%CI

Table C22: ICU LOS syntheses

	Median and Mean (Metamedian)					
Comparison	K	EST	SE	I^2	LCI	UCI
HFNO VERSUS SOT	2	Not pooled	2.26	85.28	--	--
HELMET CPAP VERSUS SOT	0					
FACEMASK CPAP VERSUS SOT	1	0.00	4.53	NA	-8.89	8.89
FACEMASK NIV VERSUS SOT	10	-1.62	0.81	74.33	-3.21	-0.03
FACEMASK NIV VERSUS HFNO	1	0.55	1.89	NA	-3.16	4.26
NIV - HEMLET versus NIV - FACEMASK	1	-3.10	1.67	NA	-6.37	0.17

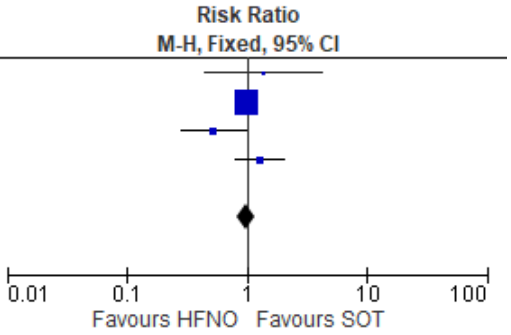
Forest plots

HFNO versus SOT

Mortality, any duration

Study or Subgroup	HFNO Events	HFNO Total	SOT Events	SOT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andino 2020	6	24	4	22	2.2%	1.38 [0.45, 4.24]
Azoulay 2018	138	388	140	388	72.5%	0.99 [0.82, 1.19]
Frat 2015	13	106	22	94	12.1%	0.52 [0.28, 0.98]
Jones 2016	35	172	24	150	13.3%	1.27 [0.79, 2.04]
Total (95% CI)		**690**		**654**	**100.0%**	**0.98 [0.83, 1.15]**
Total events	192		190			

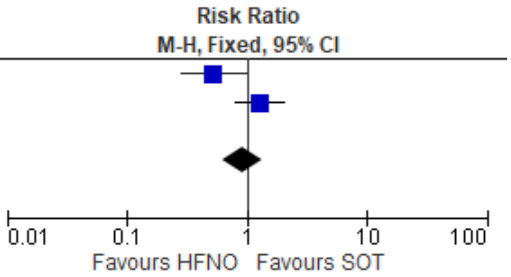
Heterogeneity: Chi² = 5.36, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 0.28 (P = 0.78)



90 d Mortality

Study or Subgroup	HFNO Events	HFNO Total	SOT Events	SOT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Frat 2015	13	106	22	94	47.6%	0.52 [0.28, 0.98]
Jones 2016	35	172	24	150	52.4%	1.27 [0.79, 2.04]
Total (95% CI)		**278**		**244**	**100.0%**	**0.92 [0.63, 1.32]**
Total events	48		46			

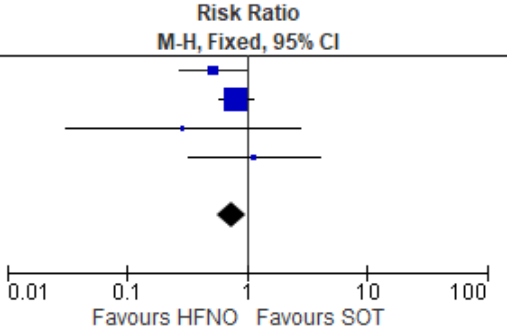
Heterogeneity: Chi² = 4.91, df = 1 (P = 0.03); I² = 80%
Test for overall effect: Z = 0.47 (P = 0.64)



IMV

Study or Subgroup	HFNO Events	HFNO Total	SOT Events	SOT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andino 2020	8	24	14	22	21.3%	0.52 [0.27, 1.00]
Frat 2015	40	106	44	94	68.0%	0.81 [0.58, 1.12]
Jones 2016	1	172	3	150	4.7%	0.29 [0.03, 2.77]
Lemiale 2015 2H	5	52	4	48	6.1%	1.15 [0.33, 4.05]
Total (95% CI)		**354**		**314**	**100.0%**	**0.74 [0.56, 0.99]**
Total events	54		65			

Heterogeneity: Chi² = 2.50, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)

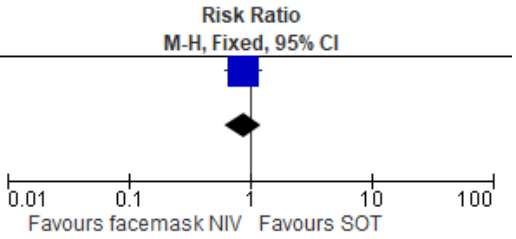


Facemask NIV versus SOT

28d Mortality

Study or Subgroup	Facemask NIV Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lemiale 2015	46	191	50	183	100.0%	0.88 [0.62, 1.25]
Total (95% CI)		**191**		**183**	**100.0%**	**0.88 [0.62, 1.25]**
Total events	46		50			

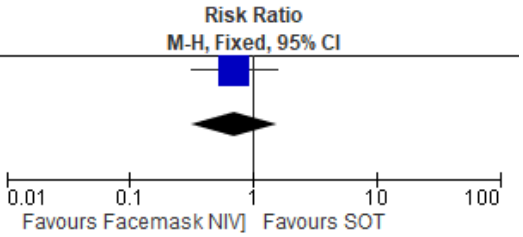
Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



60d Mortality

Study or Subgroup	Facemask NIV Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Confalonieri 1999	7	28	10	28	100.0%	0.70 [0.31, 1.58]
Total (95% CI)		**28**		**28**	**100.0%**	**0.70 [0.31, 1.58]**
Total events	7		10			

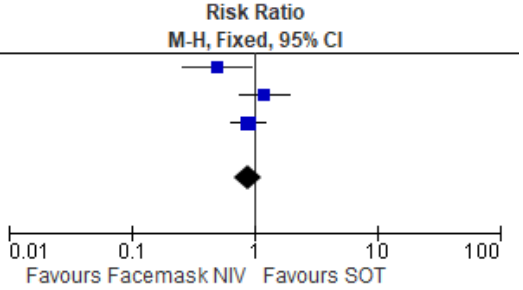
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)



90d Mortality

Study or Subgroup	Facemask NIV Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ferrer 2003	10	51	21	54	28.2%	0.50 [0.26, 0.96]
Frat 2015	31	110	22	94	32.7%	1.20 [0.75, 1.93]
Wermeke 2012	25	42	29	44	39.1%	0.90 [0.65, 1.25]
Total (95% CI)		**203**		**192**	**100.0%**	**0.89 [0.69, 1.15]**
Total events	66		72			

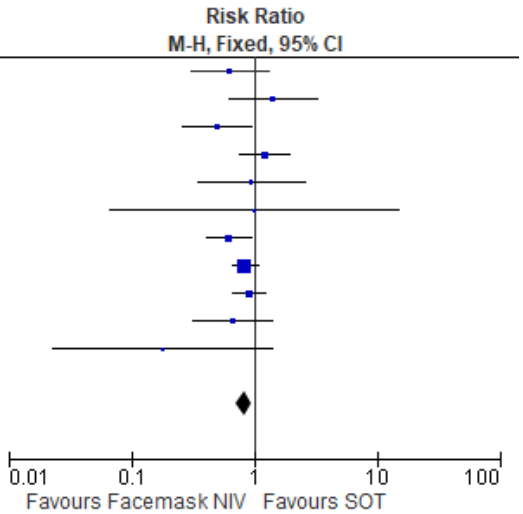
Heterogeneity: Chi² = 4.53, df = 2 (P = 0.10); I² = 56%
Test for overall effect: Z = 0.88 (P = 0.38)



Mortality, longest duration reported

Study or Subgroup	Facemask NIV Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Antonelli 2000	7	20	11	20	5.0%	0.64 [0.31, 1.30]
Confalonieri 1999	10	28	7	28	3.2%	1.43 [0.63, 3.22]
Ferrer 2003	10	51	21	54	9.3%	0.50 [0.26, 0.96]
Frat 2015	31	110	22	96	10.7%	1.23 [0.77, 1.97]
He 2019	7	105	7	99	3.3%	0.94 [0.34, 2.59]
Hernandez 2010	1	25	1	25	0.5%	1.00 [0.07, 15.12]
Hilbert 2001	13	26	21	26	9.6%	0.62 [0.40, 0.95]
Lemiale 2015	72	191	82	183	38.1%	0.84 [0.66, 1.07]
Wermeke 2012	26	42	30	44	13.3%	0.91 [0.66, 1.24]
Wysocki 1995	7	21	10	20	4.7%	0.67 [0.32, 1.41]
Zhan 2012	1	21	5	19	2.4%	0.18 [0.02, 1.41]
Total (95% CI)		**640**		**614**	**100.0%**	**0.83 [0.71, 0.96]**
Total events	185		217			

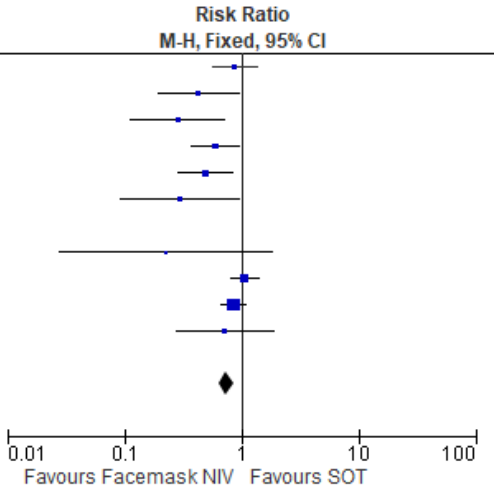
Heterogeneity: Chi² = 11.83, df = 10 (P = 0.30); I² = 15%
Test for overall effect: Z = 2.44 (P = 0.01)



IMV

Study or Subgroup	Facemask NIV Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Wysocki 1995	13	21	14	20	5.9%	0.88 [0.57, 1.38]	1995
Confalonieri 1999	6	28	14	28	5.7%	0.43 [0.19, 0.95]	1999
Antonelli 2000	4	20	14	20	5.7%	0.29 [0.11, 0.72]	2000
Hilbert 2001	12	26	20	26	8.2%	0.60 [0.38, 0.96]	2001
Ferrer 2003	13	51	28	54	11.1%	0.49 [0.29, 0.84]	2003
Hernandez 2010	3	25	10	25	4.1%	0.30 [0.09, 0.96]	2010
Wermeke 2012	0	0	0	0		Not estimable	2012
Zhan 2012	1	21	4	19	1.7%	0.23 [0.03, 1.85]	2012
Frat 2015	55	110	44	94	19.4%	1.07 [0.80, 1.42]	2015
Lemiale 2015	73	191	82	183	34.3%	0.85 [0.67, 1.09]	2015
He 2019	7	107	9	99	3.8%	0.72 [0.28, 1.86]	2019
Total (95% CI)		**600**		**568**	**100.0%**	**0.74 [0.64, 0.86]**	
Total events	187		239				

Heterogeneity: Chi² = 20.74, df = 9 (P = 0.01); I² = 57%
Test for overall effect: Z = 4.01 (P < 0.0001)

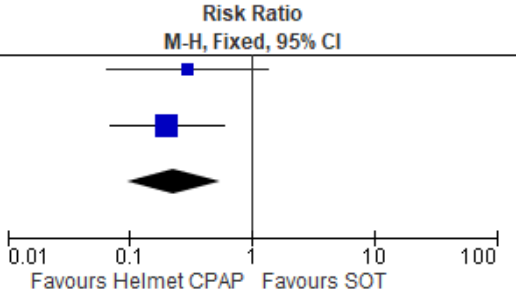


Helmet CPAP versus SOT

Mortality in hospital

Study or Subgroup	Helmet CPAP Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brambilla 2014	2	40	7	41	31.5%	0.29 [0.06, 1.33]
Cosentini 2010	0	20	0	27		Not estimable
Squadrone 2010	3	20	15	20	68.5%	0.20 [0.07, 0.59]
Total (95% CI)		**80**		**88**	**100.0%**	**0.23 [0.10, 0.55]**
Total events	5		22			

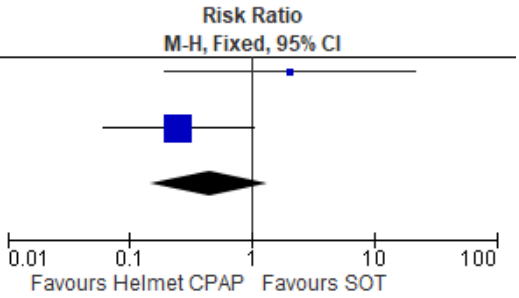
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.31 (P = 0.0009)



IMV

Study or Subgroup	Helmet CPAP Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brambilla 2014	2	40	1	41	11.0%	2.05 [0.19, 21.72]
Cosentini 2010	0	20	0	27		Not estimable
Squadrone 2010	2	20	8	20	89.0%	0.25 [0.06, 1.03]
Total (95% CI)		**80**		**88**	**100.0%**	**0.45 [0.15, 1.34]**
Total events	4		9			

Heterogeneity: Chi² = 2.24, df = 1 (P = 0.13); I² = 55%
Test for overall effect: Z = 1.44 (P = 0.15)

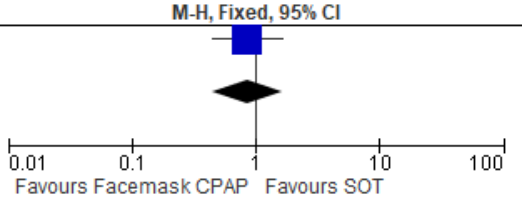


Facemask CPAP versus SOT

Mortality in hospital

Study or Subgroup	Facemask CPAP Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Delclaux 2000	13	62	15	61	100.0%	0.85 [0.44, 1.64]
Total (95% CI)		**62**		**61**	**100.0%**	**0.85 [0.44, 1.64]**
Total events	13		15			

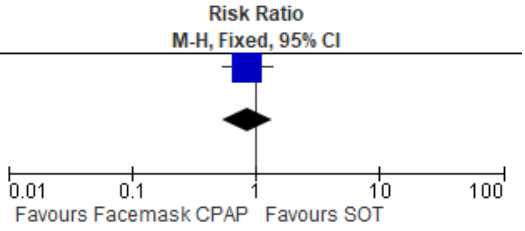
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)



IMV

Study or Subgroup	Facemask CPAP Events	Total	SOT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Delclaux 2000	21	62	24	61	100.0%	0.86 [0.54, 1.37]
Total (95% CI)		**62**		**61**	**100.0%**	**0.86 [0.54, 1.37]**
Total events	21		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)

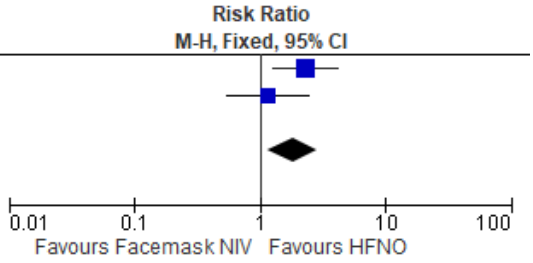


Facemask NIV versus HFNO

Mixed mortality

Study or Subgroup	Facemask NIV Events	Total	HFNO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Frat 2015	31	110	13	106	58.9%	2.30 [1.27, 4.15]
Shebl 2018	11	36	9	34	41.1%	1.15 [0.55, 2.43]
Total (95% CI)		**146**		**140**	**100.0%**	**1.83 [1.15, 2.89]**
Total events	42		22			

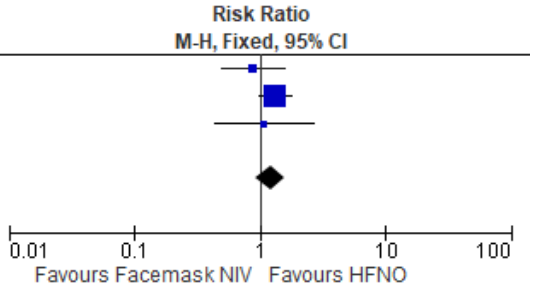
Heterogeneity: Chi² = 2.04, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.57 (P = 0.01)



IMV

Study or Subgroup	Facemask NIV Events	Total	HFNO Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Azevedo 2015	9	16	9	14	16.7%	0.88 [0.49, 1.57]
Frat 2015	55	110	40	106	70.8%	1.32 [0.97, 1.80]
Shebl 2018	8	36	7	34	12.5%	1.08 [0.44, 2.65]
Total (95% CI)		**162**		**154**	**100.0%**	**1.22 [0.94, 1.59]**
Total events	72		56			

Heterogeneity: Chi² = 1.60, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)



References

1. Teng Xb, Shen Y, Han Mf, Yang G, Zha L, Shi Jf. The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. *European journal of clinical investigation.* 2021;51:e13435-n/a.
2. Perkins GD, Ji C, Connolly BA, et al. An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19. *medRxiv.* 2021:2021.08.02.21261379.
3. Li M KC, Han H, et al. Effect of transnasal high-flow humidifying oxygen therapy for the treatment of new coronavirus pneumonia with acute respiratory failure. . *Chinese Journal of Coal Industry Medicine.* 2020;23:221-4.
4. Grieco DL, Menga LS, Cesarano M, et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. *JAMA.* 2021;325:1731-43.
5. Andino R, Vega G, Pacheco SK, et al. High-flow nasal oxygen reduces endotracheal intubation: a randomized clinical trial. *Ther Adv Respir Dis.* 2020;14:1753466620956459.
6. Antonelli M, Conti G, Bufi M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA.* 2000;283:235-41.
7. Azevedo JR, Montenegro WS, Leitao AL, Silva MM, Prazeres JS, Maranhao JP. High flow nasal cannula oxygen (hfnc) versus non-invasive positive pressure ventilation (nippv) in acute hypoxemic respiratory failure. a pilot randomized controlled trial. *Intensive Care Medicine Experimental.* 2015;3.
8. Azoulay E, Lemiale V, Mokart D, et al. Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure: The HIGH Randomized Clinical Trial. *JAMA.* 2018;320:2099-107.
9. Brambilla AM, Aliberti S, Prina E, et al. Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. *Intensive Care Med.* 2014;40:942-9.
10. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Umberto Meduri G. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med.* 1999;160:1585-91.
11. Cosentini R, Brambilla AM, Aliberti S, et al. Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. *Chest.* 2010;138:114-20.
12. Delclaux C, L'Her E, Alberti C, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomized controlled trial. *JAMA.* 2000;284:2352-60.
13. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med.* 2003;168:1438-44.
14. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med.* 2015;372:2185-96.
15. He H, Sun B, Liang L, et al. A multicenter RCT of noninvasive ventilation in pneumonia-induced early mild acute respiratory distress syndrome. *Crit Care.* 2019;23:300.

16. Hernandez G, Fernandez R, Lopez-Reina P, et al. Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia: a randomized clinical trial. *Chest.* 2010;137:74-80.
17. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med.* 2001;344:481-7.
18. Jones PG, Kamona S, Doran O, Sawtell F, Wilsher M. Randomized Controlled Trial of Humidified High-Flow Nasal Oxygen for Acute Respiratory Distress in the Emergency Department: The HOT-ER Study. *Respir Care.* 2016;61:291-9.
19. Lemiale V, Mokart D, Mayaux J, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. *Crit Care.* 2015;19:380.
20. Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA.* 2015;314:1711-9.
21. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA.* 2016;315:2435-41.
22. Shebl E, Embarak S. High-flow nasal oxygen therapy versus noninvasive ventilation in chronic interstitial lung disease patients with acute respiratory failure. *The Egyptian Journal of Chest Diseases and Tuberculosis.* 2018;67.
23. Squadrone V, Massaia M, Bruno B, et al. Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. *Intensive Care Med.* 2010;36:1666-74.
24. Wermke M, Schiemanck S, Hoffken G, Ehninger G, Bornhauser M, Illmer T. Respiratory failure in patients undergoing allogeneic hematopoietic SCT--a randomized trial on early non-invasive ventilation based on standard care hematology wards. *Bone Marrow Transplant.* 2012;47:574-80.
25. Wysocki M, Tric L, Wolff MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. A randomized comparison with conventional therapy. *Chest.* 1995;107:761-8.
26. Zhan Q, Sun B, Liang L, et al. Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. *Crit Care Med.* 2012;40:455-60.
27. Frat J-P, Ragot S, Girault C, et al. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. *The Lancet Respiratory Medicine.* 2016;4:646-52.
28. Patel BK, Wolfe KS, MacKenzie EL, et al. One-Year Outcomes in Patients With Acute Respiratory Distress Syndrome Enrolled in a Randomized Clinical Trial of Helmet Versus Facemask Noninvasive Ventilation. *Crit Care Med.* 2018;46:1078-84.
29. Thomas R, Lotfi T, Morgano GP, Darzi A, Reinap M. Update Alert 2: Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19. *Ann Intern Med.* 2020;173:W152-w3.
30. Schunemann HJ, Khabsa J, Solo K, et al. Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19: A Living Systematic Review of Multiple Streams of Evidence. *Ann Intern Med.* 2020;173:204-16.
31. Rochwerg B, Solo K, Darzi A, et al. Update Alert: Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19. *Ann Intern Med.* 2020;173:W122.
32. Lewis SR, Baker PE, Parker R, Smith AF. High-flow nasal cannulae for respiratory support in adult intensive care patients. *Cochrane Database Syst Rev.* 2021;3:CD010172.

33. Agarwal A, Basmaji J, Muttalib F, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie.* 2020;67:1217-48.
34. Radovanovic D, Coppola S, Franceschi E, et al. Mortality and clinical outcomes in patients with COVID-19 pneumonia treated with non-invasive respiratory support: A rapid review. *Journal of critical care.* 2021;65:1-8.
35. *Effectiveness of non-invasive ventilation in the treatment of acute respiratory failure due to coronavirus*: SWEDISH AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT AND ASSESSMENT OF SOCIAL SERVICES;2020.
36. *EVIDENCE CHECK: Continuous Positive Airway Pressure (CPAP) machines - What is the current advice regarding for use of CPAP as a substitute for ventilators during the* New South Wales Health, Australia;2020.
37. *COVID-19 Scientific Advisory Group Rapid Response Report - Updates on Recommended Use of Non-invasive Ventilation in AHS Acute Care Facilities During the COVID-19 Pandemic*: Alberta Health Services;2020.
38. Yasuda H, Okano H, Mayumi T, Nakane M, Shime N. Association of noninvasive respiratory support with mortality and intubation rates in acute respiratory failure: a systematic review and network meta-analysis. *Journal of Intensive Care.* 2021;9:32.
39. Ferreyro BL, Angriman F, Munshi L, et al. Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis. *JAMA.* 2020;324:57-67.
40. Baldomero AK, Melzer AC, Greer N, et al. Effectiveness and Harms of High-Flow Nasal Oxygen for Acute Respiratory Failure: An Evidence Report for a Clinical Guideline From the American College of Physicians. *Ann Intern Med.* 2021;174:952-66.
41. Lim ZJ, Subramaniam A, Ponnapa Reddy M, et al. Case Fatality Rates for Patients with COVID-19 Requiring Invasive Mechanical Ventilation. A Meta-analysis. *American journal of respiratory and critical care medicine.* 2021;203:54-66.
42. Tverring J, Akesson A, Nielsen N. Helmet continuous positive airway pressure versus high-flow nasal cannula in COVID-19: a pragmatic randomised clinical trial (COVID HELMET). *Trials.* 2020;21:994.
43. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
44. Baldomero AK, Melzer A, Greer N, Majeski BN, Macdonald R, Wilt TJ. Effectiveness and harms of high-flow nasal oxygen (HFNO) for acute respiratory failure: a systematic review protocol. *BMJ Open.* 2020;10:e034956.
45. Ferreyro BL, Angriman F, Munshi L, et al. Noninvasive oxygenation strategies in adult patients with acute respiratory failure: a protocol for a systematic review and network meta-analysis. *Syst Rev.* 2020;9:95.
46. Ferreyro BL, Angriman F, Scales DC. Noninvasive Oxygenation Strategies for Acute Hypoxemic Respiratory Failure-Reply. *JAMA.* 2020;324:1906-7.
47. McGrath S, Sohn H, Steele R, Benedetti A. Meta-analysis of the difference of medians. *Biometrical Journal.* 2020;62:69-98.