National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[H] Evidence review for respiratory support strategies

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Guideline version (Final)

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Contents

Objective

This evidence review aims to review which non-invasive respiratory support modality is most effective in adults in hospital with suspected or confirmed COVID-19 when escalating from oxygen therapy.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see Appendix A for more information). The review question for this evidence review is:

When escalating from oxygen therapy, which non-invasive modality is most effective in adults in hospital with suspected or confirmed COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

Summary of included studies

The searches for the effectiveness evidence were run on 05 01 2022. The following databases were searched: Central Register of Controlled Trials (Wiley), Embase (Ovid) MEDLINE ALL (Ovid) and the World Health Organization Covid-19 database. Full search strategies for each database are provided in Appendix B. Pre-prints were searched using EPPI reviewer v5.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The search identified 545 references. These references were screened using their titles and abstracts and 52 full text references were obtained and assessed for relevance against the criteria in the PICO.

Five studies were included in this updated evidence review. Three of these are new to this review (Ospina-Tascon et al., 2021, Nair et al., 2021 and Menga et al. 2021), and 2 RCTs were in the previous version of the evidence review (Grieco 2021 and Perkins 2022). The new studies included 2 RCTs (Ospina-Tascon et al., 2021 and Nair et al., 2022) and 1 post hoc analysis of the Grieco 2021 RCT (Menga et al. 2021). Perkins et al. (2022) was a pre-print in the original review and has now been published in JAMA. Cross checking the published study data with the preprint revealed that there were no changes to the data but the study reference has been updated in this review.

47 studies were excluded. Details of excluded studies are in Appendix E. A summary of the included studies is shown in Table 1.

Table 1: Summary of included studies

Menga et al., 2021 is a post hoc study of Grieco et al., 2021 that included dyspnoea baseline characteristics but did not include any new relevant outcomes. This detail has been included in the summary of Grieco et al 2021 below.

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Grieco et al., 2021 (HENIVOT) Oct 2020 to Dec 2020 Italy	Open label multicentre RCT	Confirmed molecular diagnosis of COVID-19.	N=109 (n=54 in NIV helmet group, 55 in HFNO group) Consecutive adults admitted in 4 ICUs in Italy due to acute hypoxaemic respiratory failure. Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) equal to or below 200, partial pressure of arterial carbon dioxide (PaCO2) equal to or lower than 45 mm Hg, absence of history of chronic respiratory failure or moderate to severe cardiac insufficiency (New York Heart Association class >II or left ventricular ejection fraction. Age: Intervention: 66 (57-72) median IQR Comparator: 63 (55-69) Gender (% female) Intervention: n=12 (22) Comparator: n=9 (16) Comorbidities:	**Helmet noninvasive ventilation (NIV)** 48- hour continuous noninvasive ventilation through the helmet interface (Dimar, Italy, or Starmed-Intersurgical, UK). NIV was delivered by a compressed gas-based ventilator connected to the helmet through a bi-tube circuit. The ventilator was set in pressure support mode, with the following settings: initial pressure support between 10 and 12 cm H2O, eventually increased to ensure a peak inspiratory flow of 100 L/min; positive end expiratory pressure between 10 and 12 cm H2O; and FIO2 titrated to obtain SpO2 between 92% and 98%. Any modification in ventilator settings and interface setup to optimize comfort and patient-ventilator interaction was allowed at the discretion of the attending physicians, but positive end	**Nasal high flow oxygen (HFNO)** Patients received nasal high-flow oxygen (Fisher and Paykel Healthcare, New Zealand) continuously for at least 48 hours. Gas flow was initially set at 60 L/min and eventually decreased in case of intolerance, FIO2 titrated to obtain peripheral oxygen saturation as measured by pulse oximetry (SpO2) between 92% and 98%, and humidification chamber was set at 37 °C or 34 °C according to the patient's comfort. HFNO could be resumed at any time if the patient experienced respiratory distress and hypoxemia (SpO2 92%). Use of NIV was not permitted in the high-flow group.	Respiratory support–free days Intubation within 28 days from enrolment Intubation within 28 days from enrolment after adjudication of intubation criteria by external experts Invasive ventilation–free days: 28 and 60 In–intensive care unit mortality In-hospital mortality Duration of stay: ICU; hospital Mortality: 28 days, 60 days

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			Hypertension Intervention: 44% Comparator: 60% Type 2 diabetes Intervention: 24% Comparator: 18% Smoking Intervention: 9% Comparator:20% Immunocompromised state Intervention: 6% Comparator: 9% Recent chemotherapy Intervention: 4% Comparator: 0% HIV Intervention: 2% Comparator: 2% Immunosuppressor therapy-kidney transplant Intervention: 0% Comparator: 4% Acute myeloid leukaemia Intervention: 0% Comparator: 2% Ulcerative colitis-immunosuppressor therapy Intervention: 0%	expiratory pressure had to be kept equal to or greater than 10 cm H2O. After interruption of noninvasive ventilation, patients underwent continuous Venturimask or high-flow nasal oxygen, according to the choice of the attending physician. Helmet noninvasive ventilation could be resumed at any time if the respiratory rate was greater than 25 breaths/min and/or SpO2 was lower than 92% Follow up: Outcomes reported at 28 and 60 days	Standard care: Continuous infusion of sedative/analgesic drugs was administered to 20 patients (37%) in the helmet group and in 10 patients (18%) in the HFNO group. Over the initial 48 hours of treatment, the mean (SD) FIO2 used in the helmet and HFNO groups were 0.54 (0.12) and 0.58 (0.9), respectively. As per clinical decision, 32 patients (60%) in the HFNO group vs 0 in the helmet group underwent prone position Use of face mask NIV before endotracheal intubation was only allowed in case of respiratory acidosis (ie, PaCO2 >45 mm Hg, with pH lev	

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			Comparator: 2% History of cancer Intervention: 8% Comparator: 0% Autism spectrum disorders Intervention: 0% Comparator: 2% Alzheimer's disease Intervention: 0% Comparator: 2% Mild or no dyspnoea Intervention: 47% Comparator: 53% Moderate-to-severe dyspnoea Intervention: 52% Comparator: 48% Key exclusions: Acute exacerbation of chronic pulmonary disease and kidney failure. Patients who had already received NIV or high-flow oxygen for more than 12 hours at the time of screening were excluded			

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Perkins et al., 2022 April 2020 to May 2020 (Early in pandemic when standard care was different) UK	Open-label, three-arm, adaptive, RCT	Known or suspected COVID-19	1277 randomisations across 48 UK hospitals N=1272 (conventional oxygen therapy n=475, CPAP n=380; HFNO n=417) Adult (≥18-years) hospitalised patients with known or suspected COVID-19 were eligible if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required. Mean age was 57.4 (95% CI, 56.7 to 58.1) years Conventional: 57.6 ± 12.7 CPAP: 56.7 ± 12.5 HFNO: 57.6 ± 13.0 (all mean, SD) Gender: 33.6% female Conventional: 163 (34.3) CPAP: 120 (31.6) HFNO: 145 (34.8) (n, %) Comorbidities: ESRF requiring RRT	**Continuous positive airway pressure (CPAP)** **High-flow nasal oxygen (HFNO)** In all participants, local policies, and clinical discretion informed decisions regarding choice of device, set-up, titration, and discontinuation of treatment. Tracheal intubation was performed when clinically indicated, based on the judgement of the treating clinician. Crossover was defined as a participant receiving CPAP or HFNO for more than 6 hours, when not randomised to that intervention, unless it was for the purpose of clinical stabilisation, as a bridge to tracheal intubation, or for palliative care. Follow up: 30 days It was anticipated that either CPAP or HFNO might be unavailable at sites on a temporary or permanent basis. As such, the randomisation system allowed the treating clinician to randomise between CPAP, HFNO, and	**Conventional oxygen therapy** Participants randomised to conventional oxygen therapy continued to receive oxygen via a face mask or nasal cannula.	Tracheal intubation or mortality: 30 days Intubation within 30 days Mortality at 30 days Admission to critical care Median time to intubation Mean length of stay in hospital Mean length of stay in critical care

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			CPAP: 0.5% HFNO: 1.4% Conventional oxygen: 1.1% Congestive heart failure CPAP: 0.5% HFNO: 1.0% Conventional oxygen: 1.1% Chronic lung disease CPAP: 17.1% HFNO: 12.5% Conventional oxygen: 13.9% Coronary heart disease CPAP: 9.0% HFNO: 6.2% Conventional oxygen: 9.3% Dementia CPAP: 1.1% HFNO: 0.2% Conventional oxygen: 0.6% Diabetes requiring medication CPAP: 22.6% HFNO: 23.5% Conventional oxygen: 19.2% Hypertension CPAP: 34.5% HFNO: 39.3% Conventional oxygen: 32.2% Uncontrolled or active malignancy CPAP: 1.8%	conventional oxygen therapy (on a 1:1:1 basis), or between a single intervention (CPAP/HFNO) and conventional oxygen therapy (on a 1:1 basis). Sites could not randomise between CPAP and HFNO only. Randomisation was stratified by site, sex, and age, and the allocation was generated by a minimisation algorithm. Crossover occurred in 58/380 (15.3%) of participants in the CPAP arm, 48/417 (11.5%) in the HFNO arm, and 112/475 (23.6%) in the conventional oxygen therapy arm.		

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			HFNO: 2.4% Conventional oxygen: 1.5% Morbid obesity (BMI >35) CPAP: 16.3% HFNO: 19.4% Conventional oxygen: 15.8% Key exclusions: Patients with an immediate (<1 hour) need for invasive ventilation, known pregnancy, or planned withdrawal of treatment. A contraindication to an intervention, based on the judgement of the treating clinician, precluded randomisation to that trial arm.			
Ospina-Tascon et al., 2021 [New] August 2020 to Feb 2021 Columbia	RCT	Suspected or confirmed infection with SARS-CoV-2 (confirmation via reverse transcriptase–polymerase chain reaction test from a	N=199 (High flow oxygen therapy n=99, conventional oxygen therapy n=100) in emergency and intensive care units in 3 hospitals in Colombia. Adult (≥18-years); suspected or confirmed infection with SARS-CoV-2 (confirmation via reverse transcriptase–polymerase chain reaction test from a nasopharyngeal swab); acute respiratory failure with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) of less than 200, accompanied by clinical signs of respiratory distress (eg, use of accessory muscles and	**High-flow oxygen therapy** The high-flow oxygen therapy was continuously applied until intubation or when criteria for weaning of high flow oxygen therapy were achieved, namely, improvement in clinical signs of respiratory distress, a PaO2/FIO2 ratio higher than 200, and ability to maintain SpO2values of 92% or greater with less than 9 L/min of conventional oxygen therapy. Follow up: 28 days	**Conventional oxygen therapy.** Oxygen was applied continuously through any low-flow oxygen device or combination thereof (nasal prongs, mask with or without oxygen reservoir, Venturimask systems). Rates of gas flow and FIO2 were adjusted to maintain SpO2 values of 92% or greater until patient intubation or recovery.	Intubation within 28 days Clinical recovery within 28 days Time to clinical recovery

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		nasopharyngeal swab)	respiratory rate greater than 25/min); and less than 6 hours elapsed since fulfilling the criteria of acute respiratory failure. Age: High flow oxygen therapy: 60 (95% CI, 50 to 69) years Conventional: 59 (95% CI, 49 to 67) years Comorbidities: Hypertension Intervention: 35% Comparator: 44% Diabetes Intervention: 18% Comparator: 20% Liver cirrhosis (Child-Pugh class A-B)f Intervention: 35% Comparator: 44% Chronic obstructive pulmonary disease Intervention: 3% Comparator: 1% Chronic heart failure Intervention: 3% Comparator: 4% Chronic kidney disease			Intubation within 7 days Intubation within 14 days Ventilation-free days at day 28 Length of stay: ICU; Hospital Mortality at day 14 Mortality at day 28 Serious adverse events: Cardiac arrest; Suprasupraventricular tachycardia or ventricular arrhythmia; Atelectasis Other reported adverse events: Suspected bacterial pneumonia; Bacteremia

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			Intervention: 0% Comparator: 1% Cancer Intervention: 1% Comparator: 0% Key exclusions: Need for immediate endotracheal intubation; a partial pressure of arterial carbon dioxide greater than 55 mm Hg; pregnancy; high suspicion or confirmation of acute cardiogenic pulmonary oedema; history of or current left ventricular ejection fraction of less than 45%; history of chronic heart failure (New York Heart Association class III-IV)16; clinical suspicion or confirmation of peripheral demyelinating disease; history of advanced chronic obstructive pulmonary disease (Global Initiative for ChronObstructive Lung Disease grade C-D)17 or hospitalisation due to chronic obstructive pulmonary disease decompensation within the last year; advanced liver cirrhosis (Child-Pugh class C)18; anatomical or other conditions precluding the use of a high-flow nasal cannula; do-not-intubate or do-not resuscitate orders; imminent death; and refusal of			

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			study participation by a patient or their next of kin.			
Nair et al., 2021 [New] Aug 2020 to Dec 2020 New Delhi, India	RCT	Laboratory-confirmed diagnosis of COVID-19 pneumonia	N=109 (High flow nasal canula n=55; NIV n=54) in an ICU of a tertiary care teaching hospital in New Delhi, India Adult subjects of age 18–75 years with laboratory-confirmed diagnosis of COVID-19 pneumonia, presenting with severe COVID-19 pneumonia, who failed oxygen therapy by face mask, were included in this study Age: HFNC: 57 (95% CI, 48 to 65) years NIV: 57.5 (95% CI, 47 to 64) years Gender (% female): HFNC: 11 (20) NIV: 19 (35.2) Comorbidities: Diabetes mellitus HFNC: 30.90%	**High flow nasal canula** The initial gas flow for the high flow nasal canula was set at 50 L/min and FIO2 of 1.0. The flow and FIO2 were subsequently adjusted between 30–60 L/min and 0.5–1.0, respectively, to maintain SpO2 of 94% or more. Follow up: 28 days Standard care: Clinical management of all subjects including fluid therapy, monitoring of vitals, baseline blood investigations, chest radiograph, and point-of care ultrasound was as per standard institute protocol. All subjects received supportive drug therapy as per current institutional protocol. Awake prone positioning was encouraged to subjects and	**Non-invasive ventilation** For the NIV arm: ICU ventilator with the setting of pressure support (PS) of 10–20 cm H2O adjusted with the aim of obtaining an expired tidal volume of 7–10 mL per kilogram of predicted body weight and PEEP 5–10 cm H2O and FIO2 0.5–1.0 titrated to target SpO2 > 94%. Subjects allocated to NIV arm were applied to NIV with either mask/helmet device connected to an ICU ventilator	Mortality at 30 days Intubation within 30 days Tracheal intubation or mortality at 30 days Intubation within 7 days Intubation within 48 hours

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			NIV: 29.62% Hypertension HFNC: 30.90% NIV: 37.03% Chronic kidney disease HFNC: 7.27% NIV: 22.22% Chronic liver disease HFNC: 1.81% NIV: 1.85% Coronary artery disease HFNC: 18.18% NIV: 12.96% Key exclusions: Hemodynamic instability and requirement of high-dose vasopressor therapy; pregnancy; COPD/chronic respiratory failure; morbid obesity; patients with urgent requirement of invasive mechanical ventilation, severe hypoxia (SpO2 < 90% with frequency > 40 breaths/min for > 10 min), severe hemodynamic instability (mean arterial pressure < 65 mm Hg in spite of high-dose noradrenaline support) with altered mentation, Glasgow coma scale score < 8, or cardiac arrest were excluded.	allowed at the discretion of attending ICU physician		

Results

When escalating from oxygen therapy, which non-invasive modality is most effective in adults in hospital with suspected or confirmed COVID-19?

The included RCTs allowed 4 comparisons of respiratory support modalities to be made:

- Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins et al., 2022)
- High-flow nasal oxygen (HFNO) versus conventional oxygen (Perkins et al., 2022; Ospina-Tascón et al., 2021)
- HFNO versus non-invasive ventilation (Nair et al., 2021)
- Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco et al., 2021)

As the comparisons differed between studies it was only possible to meta-analyse the included data for the HFNO versus conventional oxygen comparison.

Summary of outcomes

Comparison 1: CPAP versus conventional oxygen (Perkins et al., 2022)

There was no new data to update these outcomes. Although no new data was included for this comparison in this update, we changed the results from odds ratios (ORs) to risk ratios (RRs) for consistency with the other comparisons. This change did not alter the direction of effect for any outcome.

Findings

Evidence indicates that that the use of continuous positive airway pressure (CPAP) may have some treatment benefits, including intubation outcomes, in people with COVID-19 and respiratory failure.

What is the evidence informing this conclusion?

Evidence comes from 1 randomised controlled trial (RCT) of patients with COVID-19 and respiratory failure (Perkins et al., 2022).

The RCT allowed 1 comparison of respiratory support modalities to be made:

Continuous positive airway pressure (CPAP) versus conventional oxygen (Perkins 2022)

Because there was only 1 study, it was not possible to meta-analyse the included data.

Publication status

Perkins 2022 is a full publication.

Study characteristics

One RCT included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and when tracheal intubation was considered a clinically appropriate treatment option if treatment escalation was required (Perkins 2022).

Mean age in Perkins (2022) 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%. The total number of participants was 737.

What are the main results?

Compared with conventional oxygen, CPAP significantly reduces tracheal intubation or mortality at 30 days (RR 0.83 95% CI 0.69 – 0.99)) in people with COVID-19 and acute respiratory failure. Median time to intubation (Hazard Ratio (adjusted): 0.67 (95% CI 0.52 - 0.86)) was significantly delayed and admissions to critical care (RR 0.88 (95% CI 0.78 - 1.00)) was significantly reduced in the group receiving CPAP compared with conventional oxygen in people with COVID-19.

No difference was observed between CPAP and conventional oxygen for mortality, length of hospital stay and length of critical care stay.

Our confidence in the results

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is moderate for tracheal intubation or mortality (30 days), tracheal intubation (30 days), median time to intubation and admission to critical care (due to serious risk of bias).

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for mortality, length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision).

Comparison 2: HFNO versus conventional oxygen (Perkins 2022, Ospina-Tascon 2021)

In this update we included data from Ospina-Tascon 2021 for the following outcomes:

- Mortality at 28 or 30 days
- Intubation within 28 or 30 days
- Median length of stay in hospital
- Median length of stay in critical care

There was no new data for the following outcomes:

- Composite outcome: Tracheal intubation or mortality at 30 days
- Median time to intubation
- Admission to critical care
- Mean length of stay in hospital
- Mean length of stay in critical care

Findings

The evidence does not support the use of HFNO as a main treatment option.

What is the evidence informing this conclusion?

Evidence comes from 2 randomised controlled trials (RCTs) of patients with COVID-19 and respiratory failure (Perkins 2022 and Ospina-Tascon 2021).

The 2 included RCTs allowed 1 comparison of respiratory support modalities to be made:
HFNO versus conventional oxygen (Perkins 2022 and Ospina-Tascon 2021)

It was possible to meta-analyse Perkins 2022 and Ospina-Tascon 2021 for the HFNO versus conventional oxygen comparison.

Publication status

Perkins 2022 and Ospina-Tascon 2021 are both full publications.

Study characteristics

Two RCTs included adult (≥18-years) hospitalised patients with known or suspected COVID-19 if they had acute respiratory failure. One of these defined respiratory failure as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least 0.4, and when tracheal intubation was considered a clinically appropriate treatment option if treatment escalation was required (Perkins 2022). The other RCT defined respiratory failure as participants having a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) of less than 200, accompanied by clinical signs of respiratory distress (Ospina-Tascon 2021).
The mean age in Perkins 2022 was 57.4 (95% CI, 56.7 to 58.1) years with the proportion of women being 33.6%. The total number of participants was 785.The mean age in Ospina-Tascon 2021 was 59 to 60 years (49-69) with the proportion of women being 28-37%. The total number of participants was 199.

What are the main results?

No difference was observed between HFNO and conventional oxygen for any outcome measured. These outcomes were: mortality at 30 days, tracheal intubation or mortality at 30 days, intubation within 30 days, median time to intubation, admission to critical care, mean length of stay in hospital, and mean length of stay in critical care.

Our confidence in the results

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for tracheal intubation or mortality (30 days), median time to intubation, admission to critical care, mortality (28-30 days), length of hospital stay and length of critical care stay (due to serious risk of bias and serious imprecision). The certainty of the evidence was very low for tracheal intubation (28-30 days) (due to serious risk of bias, serious inconsistency, and serious imprecision).

Comparison 3: Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco et al., 2021)

Findings

There was no new evidence identified at this update. Existing evidence indicates that that the use of helmet NIV followed by HFNO may have some treatment benefits, including intubation outcomes and invasive ventilation free days, in people with COVID-19 and respiratory failure compared with HFNO alone.

What is the evidence informing this conclusion?

Evidence comes from 1 randomised controlled trial (RCT) of patients with COVID-19 and respiratory failure (Grieco 2021).
The 1 included RCT allowed 1 comparison of respiratory support modalities to be made:
Helmet non-invasive ventilation followed by HFNO versus HFNO (Grieco 2021)

Because there was only 1 RCT, it was not possible to meta-analyse the included data.

Publication status

Grieco et al. (2021) is a full publication.

Study characteristics

One RCT included adults with confirmed COVID-19 adults admitted in the ICU due to acute hypoxaemic respiratory failure (Grieco 2021).
The median and interquartile range for age in the Greico 2021 RCT was 66 years (57-72) in the intervention group and 63 years (55-69) in the comparator group and the proportion of women was 19%. The total number of participants was 109.

What are the main results?

Compared with HFNO, helmet NIV followed by HFNO significantly reduces intubation within 28 days from enrolment (RR 0.58 (95% CI 0.36 - 0.95)), intubation within 28 days from enrolment after adjudication of intubation criteria by external experts (RR 0.55 (95% CI 0.33 - 0.9)) and invasive ventilation free days at 28 days (Mean difference 3 more (95% CI 0 more - 7 more)).
No difference was observed between helmet non-invasive ventilation followed by HFNO and HFNO for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (at 60 days), duration of hospital stay and duration of ICU stay.

Our confidence in the results

In patients with COVID-19 with acute respiratory failure, certainty of the evidence is low for intubation within 28 days from enrolment, intubation within 28 days from enrolment after adjudication of intubation criteria by external experts and invasive ventilation free days (28 days) (due to serious risk of bias and serious indirectness).
In patients with COVID-19 with acute respiratory failure, certainty of the evidence is very low for mortality at 28 and 60 days, in-hospital mortality, intensive care mortality, respiratory support free days, invasive ventilation free days (60 days), duration of hospital stay and duration of ICU stay.

Comparison 4: HFNO versus NIV (Nair 2021)

In this update we included data from Nair 2021 for the following outcomes:

- In-hospital mortality at 30 days

- Composite outcome: Tracheal intubation or mortality at 20 days
- Intubation within 48 hours
- Intubation within 7 days
- Median (IQR) length of stay in hospital

Findings

Evidence indicates that high-flow nasal oxygen (HFNO) may have some treatment benefits, including tracheal intubation or mortality at 30 days and intubation within 7 days, in people with COVID-19 who have failed oxygen therapy by face mask, compared with NIV.

What is the evidence informing this conclusion?

Evidence comes from one randomised controlled trial (RCT) of patients with COVID-19 who have failed oxygen therapy by face mask (Nair 2021). This RCT allowed 1 comparison of respiratory support to be made:
High-flow nasal oxygen (HFNO) versus non-invasive ventilation (NIV) (Nair 2021)

Meta-analysis was not possible because there was only 1 study.

Publication status

Nair et al. (2021) is a full publication.

Study characteristics

One RCT included adult patients (18-75 years) in an intensive care unit (ICU) with known COVID-19 if they had presented with severe COVID-19 pneumonia and had failed oxygen therapy by face mask (Nair 2021).
The mean age in Nair 2021 was 57 years (95% CI 48 to 65) in the HFNO group and 57.5 years (95% CI 47 to 64) in the NIV group with the proportion of women being 20-35%. The total number of participants was 109.

What are the main results?

Compared with NIV, HFNO significantly reduced tracheal intubation or mortality at 30 days (Hazard Ratio 0.51 (95% CI 0.28 to 0.93)) in people who have failed oxygen therapy by face mask. Intubation within 7 days (RR 0.59 (95% CI 0.35 to 0.99)) was significantly reduced in the group receiving HFNO compared with NIV in people who have failed oxygen therapy by face mask.
No difference was observed between HFNO and NIV for in-hospital mortality at 30 days, intubation within 48 hours, or median length of stay in hospital.

Our confidence in the results

In patients with COVID-19 who had failed oxygen therapy by face mask, certainty of the evidence is moderate for tracheal intubation or morality (30 days), intubation (7 days), and length of stay in hospital (due to serious risk of bias). The certainty of the evidence was low for in-hospital mortality (30 days), and intubation (48 hours) (due to serious risk of bias and serious imprecision).

Evidence to decision

Benefits and harms

CPAP

The panel discussed the findings from 1 randomised controlled trial (Perkins 2022) included in the evidence review.

The panel agreed that the evidence from Perkins 2022 shows that using continuous positive airway pressure (CPAP) reduces the number of people who need invasive ventilation and admission to critical care. They also noted that evidence from Perkins 2022 suggests there is a small increase in the number of serious adverse events with CPAP compared with conventional oxygen therapy. However, they considered that there are uncertainties with the available evidence, including evidence on standard care, staffing ratios, and where people had CPAP and which staff gave it.

The panel agreed that these uncertainties warranted a recommendation to consider offering CPAP to people with COVID-19 when they:

- have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 40% or more, and
- escalation to invasive mechanical ventilation is appropriate but not immediately needed.

The panel noted that sometimes people who experience an increased effort of breathing have CPAP or high flow nasal oxygen. However, this indication is generally not included in studies because it is difficult to measure this in an objective way. The panel noted that it is important for staff to have skills and competencies in CPAP and that people have CPAP in an appropriate setting. They provided a consensus recommendation to support this.

No evidence was found on reviewing and monitoring people having continuous positive airway pressure (CPAP). However, the panel noted that it is important that staff have skills and competencies in CPAP and that people have CPAP in an

appropriate setting. They provided a consensus recommendation to support this. The panel discussed the importance of ensuring that CPAP is not used for longer than it is needed. They strongly emphasised the importance of regularly reviewing people having CPAP (for example every 12 hours) to ensure that it is promptly recognised when treatment has failed and that treatment is escalated when needed. They made a consensus recommendation to support this.

The panel agreed not to define treatment failure to allow for individual clinical decision making.
The panel also made a consensus recommendation to optimise pharmacological and non-pharmacological management strategies in people who need non-invasive respiratory support.

HFNO

The panel discussed the findings from 4 randomised controlled trials (Perkins 2022, Ospina-Tascon 2021, Grieco 2021 and Nair 2021) included in the evidence review. They noted that aggregated evidence from Perkins 2022 and Ospina-Tascon 2021 does not show that using high-flow nasal oxygen (HFNO) has any benefits compared with conventional oxygen therapy.

They noted that evidence from Nair 2021 shows that HFNO reduces intubation within 30 days and 7 days compared to non-invasive ventilation (NIV). They noted that evidence from Grieco 2021 shows that helmet NIV followed by HFNO reduces intubation within 28 days from enrolment compared to HFNO alone. However, the panel agreed that these comparisons were not directly applicable because NIV and helmet NIV are not standards of care in the UK and there is uncertainty regarding how NIV was delivered in Nair 2021. They also noted that there was a lack of patient-reported outcome measures. The panel noted that the clinical situation has changed since these trials were conducted because there is now a high proportion of vaccinated individuals and a different COVID-19 variant (Omicron) is now prevalent and may have different clinical characteristics to previous strains.

They made a recommendation to not routinely offer HFNO as the main form of respiratory support for people with respiratory failure due to COVID-19 in whom escalation to invasive mechanical ventilation would be appropriate.

Although there is no evidence on treatment breaks from continuous positive airway pressure (CPAP), the panel noted this was an important consideration. The panel acknowledged that although high-flow nasal oxygen should not be routinely offered as the main form of respiratory support, it may be considered in some situations. This includes when maximal conventional oxygen is not maintaining the person's target oxygen saturations and they do not need immediate intubation. It also includes people having CPAP who cannot tolerate CPAP, or who need a break from CPAP (such as at mealtimes), humidified oxygen or weaning from CPAP. They made a consensus recommendation to support this

Certainty of the evidence

The panel were aware that the certainty of the evidence for outcomes in the Perkins 2022, Grieco 2021, and Nair 2021 studies ranged from moderate to very low mostly because of risk of bias, and imprecision because of confidence intervals crossing the line of no effect.

Values and preferences

Lay members noted that people with COVID-19 may have different opinions on how acceptable non-invasive respiratory support is. Some people may be apprehensive of its use and others may be willing to accept it as an available treatment option. Patient preferences should be considered in a shared discussion. For example, the panel noted that some people tolerate high flow nasal oxygen better than continuous positive airway pressure (CPAP).

The panel agreed that treatment plans, preferences and wishes should be discussed with patients, families, and carers before starting non-invasive respiratory support. Therefore, the panel concluded that it was important to augment the recommendations in the guideline section 'Deciding when to escalate treatment' by adding links to further advice from professional organisations. The panel also

considered that care of people who will not have treatment escalation should be supported by provision of a link to existing recommendations on pharmacological and non-pharmacological treatment option.

The panel noted that outcomes, such as symptom control, would be important to people with COVID-19 and should be reported in future trials provided there are adequate staff and personal protective equipment to facilitate measurement. The panel made a research recommendation to explore the role of high-flow nasal oxygen in reducing breathlessness compared with standard care or conventional oxygen therapy, to help improve the evidence base in this area.

Resources

CPAP

The panel considered that using continuous positive airway pressure (CPAP) for people with COVID-19 in appropriate settings outside of the intensive care unit (ICU) has the potential to increase available ICU capacity. Avoiding the need for invasive mechanical intubation may also result in cost savings and avoid adverse outcomes from intubation. However, the panel were mindful that CPAP must be given by staff who have skills and competencies in CPAP, be accompanied by careful review, prompt recognition of when treatment has failed, and have a management plan should the CPAP fail. Resource use was not assessed for reviewing and monitoring people having CPAP. However, the panel noted that review and monitoring may result in additional use of staff resources.

HFNO

The panel indicated that high-flow nasal oxygen (HFNO), in particular, consumes a large amount of oxygen. Therefore, when oxygen supplies are low, this should be taken into account when deciding whether to use HFNO.

Cost effectiveness was not assessed as part of the evidence review.

Equity

HFNO

The panel noted that in Perkins 2022, the composite outcome of tracheal intubation or mortality within 30 days was not statistically significant for any particular ethnic group.

The scope of this evidence review was limited to adults and so no evidence in children and young people was included.

The panel noted that some people, including those with cognitive impairment for example, may find it difficult to tolerate non-invasive respiratory support. As such, patient preferences should be considered in a shared discussion with the person and their family or carer.

In Perkins 2022, hypoxaemia was defined by reference to pulse oximetry. The MHRA has issued advice on the use of pulse oximeters and the factors which may affect their accuracy (which include skin colour).

Acceptability

CPAP

The panel discussed that some people find continuous positive airway pressure (CPAP) uncomfortable. The panel also commented that some people may find it difficult to tolerate non-invasive respiratory support. They noted that high-flow nasal oxygen would allow people having CPAP to take treatment breaks for mealtimes and when CPAP is being gradually reduced. They made a consensus recommendation to support this. The panel proposed a research recommendation to explore which treatment methods are effective for weaning people with COVID-19 from CPAP and the acceptability and safety of these methods.

The panel also commented on the importance of discussing and reaching a shared decision with the person on the modality of CPAP used (for example, mask or helmet).

HFNO

The panel acknowledged that although high-flow nasal oxygen should not be routinely offered as the main form of respiratory support, it may be considered in some situations, which are provided in a consensus recommendation to consider using high-flow nasal oxygen under certain conditions. The panel also proposed a research recommendation to explore which treatment methods are effective for weaning people with COVID-19 from CPAP and the acceptability and safety of these methods.

Feasibility

CPAP

Continuous positive airway pressure (CPAP) is an established treatment in the NHS. However, the panel advised that context-specific factors influence when CPAP may be used, for example staff skills and competencies, staffing ratios and the availability of different CPAP interfaces, so CPAP use may vary in practice.

HFNO

High-flow nasal oxygen is an established treatment in the NHS. It may be considered in certain situations as outlined the recommendation 3.2.16 to consider use of high-flow nasal oxygen.

Appendices

Appendix A: PICO table

PICO table

When escalating from oxygen therapy, which non-invasive modality is most effective in adults in hospital with suspected or confirmed COVID-19?

Population	Adults in hospital with suspected or confirmed COVID-19 who require escalation of respiratory support from oxygen therapy only
Intervention	Non-invasive respiratory support: • High-flow nasal oxygen (HFNO) • Continuous positive airway pressure therapy (CPAP) • BiLevel non-invasive ventilation
Comparators	Standard care Each other
Outcomes	1) Mortality 2) Time to recovery 3) Length of hospital stay 4) Risk of intubation/time to intubation 5) Admission to ICU 6) Composites such as ventilator-free days or organ support-free days 7) Complications (e.g. pneumothorax, pneumomediastinum, haemodynamic instability or secondary bacterial infection)
Subgroups	• Adults > 50 years • Children <12 years of age • Disease severity • Gender • Ethnic background • Deprivation / socioeconomic status • Frailty score • Patients appropriate for intubation or not • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset
Study design	RCTs or systematic reviews of RCTs are preferable If no RCTs are available may consider retrospective or prospective cohort studies with a control group.

Appendix B: Literature search strategy/Data source

Search design and peer review

This search was developed in compliance with section 8 of Appendix L of the NICE manual: NICE (15 October 2020) Developing NICE guidelines: the manual. Process and methods [PMG20]. Appendix L: Interim process and methods for guidelines developed in response to health and social care emergencies

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 5th January 2022. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.
NICE's approach to retrieving preprints has evolved throughout the pandemic:

- Prior to 20th April 2020 MedRxiv and BioRxiv were searched directly.
- From 20th April 2020 an automated process was used to download the entire MedRxiv and BioRxiv COVID-19 and SARS-COV-2 collection into EPPI Reviewer 5 and update the results daily. Individual topic searches were conducted within EPPI Reviewer to get round the limitations of the native search functionality in MedRxiv and BioRxiv.
- From 19th August 2021, results from additional preprint servers were added to the EPPI Reviewer database on a weekly basis. The additional results were sourced from the aggregator sites Europe PMC and the NIH Office of Portfolio Analysis COVID-19 database. These sites index multiple preprint servers, including Arxiv, MedRxiv, BioRxiv, Research Square, SSRN and preprints.org. The NIH database is pre-sifted for COVID-19 related references. Europe PMC is broader, and so we initially used their stock strategy to narrow the results down to a subset that were related to COVID-19. References added to the aggregator sites from the 10th August 2021 were downloaded, but searches of these sources were not backdated further.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search updates a previous search performed in the NICE COVID-19 Surveillance EPPI Review. This EPPI review covers journal articles, reports, policies, guidelines, pre-prints and other documents published on COVID-19 or SARS-CoV-2 since 16 March 2020

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude letters, comments, editorials, case reports and animal studies were applied in adherence to standard NICE practice and the review protocol.
The search was limited from 1st August 2021 to 31st January 2022 as defined in the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters

- Covid-19 filter

The development of NICE's main database search strategy for Covid-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. MedRxiv preprint. https://doi.org/10.1101/2021.06.11.21258749

- RCT filters:
    - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.
      Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

    - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

      Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
    - Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Main search – Databases

Database	Date searched	Database platform	Segment	No. of results
MEDLINE ALL	05/01/2022	Ovid	Ovid MEDLINE(R) ALL <1946 to January 04, 2022>	161
Embase	05/01/2022	Ovid	Embase <1974 to 2022 January 04>	323
Cochrane - CENTRAL	05/01/2022	Wiley	*Cochrane* Central Register of Controlled Trials Issue 12 of 12, December 2021	141
MedRxiv/BioRxiv/Europe PMC/NIH Portfolio Preprints [EPPI review]	05/01/2022	N/A	last modified 05/01/2022	53
WHO Covid-19 Database	05/01/2022	N/A	N/A	77

Search strategy history

Database name: MEDLINE ALL

1 SARS-CoV-2/ or COVID-19/ (131175)
2 (corona* adj1 (virus* or viral*)).ti,ab,kw,kf. (4581)
3 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf. (73293)
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf. (223436)
5 or/1-4 (229603)
6 Oxygen Inhalation Therapy/ (15448)
7 Noninvasive Ventilation/ (3031)
8 Continuous Positive Airway Pressure/ (8326)
9 ((noninvasive or non-invasive or cannula* or mask* or reservoir*) adj4 (ventilat* or respirat* or oxygen*)).ti,ab. (17855)
10 (respirat* adj2 (support* or fail*)).ti,ab. (42179)

11 (high flow* adj3 (oxygen* or cannula*)).ti,ab. (2714)
12 (HFNO or CPAP or BiPAP or BPAP).ti,ab. (9932)
13 ((continu* or bilevel* or bi-level or biphasic or bi-phas*) adj2 positive airway pressure).ti,ab. (10988)
14 helmet*.ti,ab. (5971)
15 or/6-14 (88405)
16 5 and 15 (5098)
17 randomized controlled trial.pt. (554956)
18 randomi?ed.mp. (977890)
19 placebo.mp. (231823)
20 or/17-19 (1039817)
21 (MEDLINE or pubmed).tw. (261340)
22 systematic review.tw. (208991)
23 systematic review.pt. (181025)
24 meta-analysis.pt. (149961)
25 intervention*.ti. (173346)
26 or/21-25 (566190)
27 20 or 26 (1454134)
28 16 and 27 (578)
29 limit 28 to ed=20210801-20220131 (99)
30 limit 28 to dt=20210801-20220131 (130)
31 29 or 30 (169)
32 (Recovery* respiratory support* or recovery* RS* or ISRCTN16912075 or ISRCTN 16912075 or IRAS282338 or "282338").af. (60)
33 5 and 32 (2)
34 (31 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (159)
35 33 or 34 (161)

Database name: Embase

1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (186022)
2 (corona* adj1 (virus* or viral*)).ti,ab,kw. (4178)
3 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab,kw. (64981)
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw. (226290)
5 or/1-4 (242545)
6 assisted ventilation/ (18693)
7 oxygen therapy/ (35775)
8 exp noninvasive ventilation/ (17316)
9 continuous positive airway pressure/ (3592)
10 bilevel positive airway pressure/ (936)
11 ((noninvasive or non-invasive or cannula* or mask* or reservoir*) adj4 (ventilat* or respirat* or oxygen*)).ti,ab. (29736)
12 (respirat* adj2 (support* or fail*)).ti,ab. (70685)
13 (high flow* adj3 (oxygen* or cannula*)).ti,ab. (4967)
14 (HFNO or CPAP or BiPAP or BPAP).ti,ab. (19809)
15 ((continu* or bilevel* or bi-level or biphasic or bi-phas*) adj2 positive airway pressure).ti,ab. (16108)
16 helmet*.ti,ab. (7235)
17 or/6-16 (166129)
18 5 and 17 (11706)
19 random:.tw. (1738844)
20 placebo:.mp. (486799)
21 double-blind:.tw. (226296)

22 or/19-21 (2003904)
23 (MEDLINE or pubmed).tw. (325400)
24 exp systematic review/ or systematic review.tw. (391179)
25 meta-analysis/ (233551)
26 intervention*.ti. (228989)
27 or/23-26 (794013)
28 22 or 27 (2550045)
29 18 and 28 (1249)
30 limit 29 to dc=20210801-20220131 (448)
31 (Recovery* respiratory support* or recovery* RS* or ISRCTN16912075 or ISRCTN 16912075 or IRAS282338 or "282338").af. (82)
32 5 and 31 (7)
33 (30 and english.lg.) not (letter or editorial or conference).pt. not (nonhuman/ not human/) not "case report".sh. (316)
34 32 or 33 (323)

Database name: Central Register of Controlled Trials

#1 MeSH descriptor: [SARS-CoV-2] this term only 627
#2 MeSH descriptor: [COVID-19] this term only 1042
#3 (corona* near/1 (virus* or viral*)):ti,ab,kw 292
#4 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 614
#5 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or covid19 or covid-19 or covid):ti,ab,kw 9401
#6 {OR #1-#5} 9453
#7 MeSH descriptor: [Oxygen Inhalation Therapy] this term only 1279
#8 MeSH descriptor: [Noninvasive Ventilation] this term only 317
#9 MeSH descriptor: [Continuous Positive Airway Pressure] this term only 1222
#10 ((noninvasive or non-invasive or cannula* or mask* or reservoir*) near/4 (ventilat* or respirat* or oxygen*)):ti,ab 6244
#11 (respirat* near/2 (support* or fail*)):ti,ab 5808
#12 (high flow* near/3 (oxygen* or cannula*)):ti,ab 1837
#13 (HFNO or CPAP or BiPAP or BPAP):ti,ab 5284
#14 ((continu* or bilevel* or bi-level or biphasic or bi-phas*) near/2 positive airway pressure):ti,ab 4097
#15 helmet*:ti,ab 517
#16 {OR #7-#15} 16893
#17 #6 and #16 with Publication Year from 2021 to 2022, in Trials 387
#18 ((Recovery* next respiratory next support*) or (recovery* next RS*) or (ISRCTN16912075) or (ISRCTN 16912075) or IRAS282338 or "282338"):ti,ab 9
#19 #6 and #18 with Publication Year from 2021 to 2022, in Trials 0
#20 #17 or #19 387
#21 "conference":pt or (clinicaltrials or trialsearch):so 582582
#22 #20 not #21 141

Database name: Pre-prints - medRxiv and bioRxiv/ Europe PMC/NIH Portfolio

These were searched via EPPI reviewer v5 using filters Title and Abstract HAS ALL and AND Title and Abstract HAS ANY.
Search terms combined terms non; invasive, noninvasive, CPAP, HFNO, BiPAP, BPAP, positive airway pressure, oxygen, ventilation, helmet, high flow, cannula

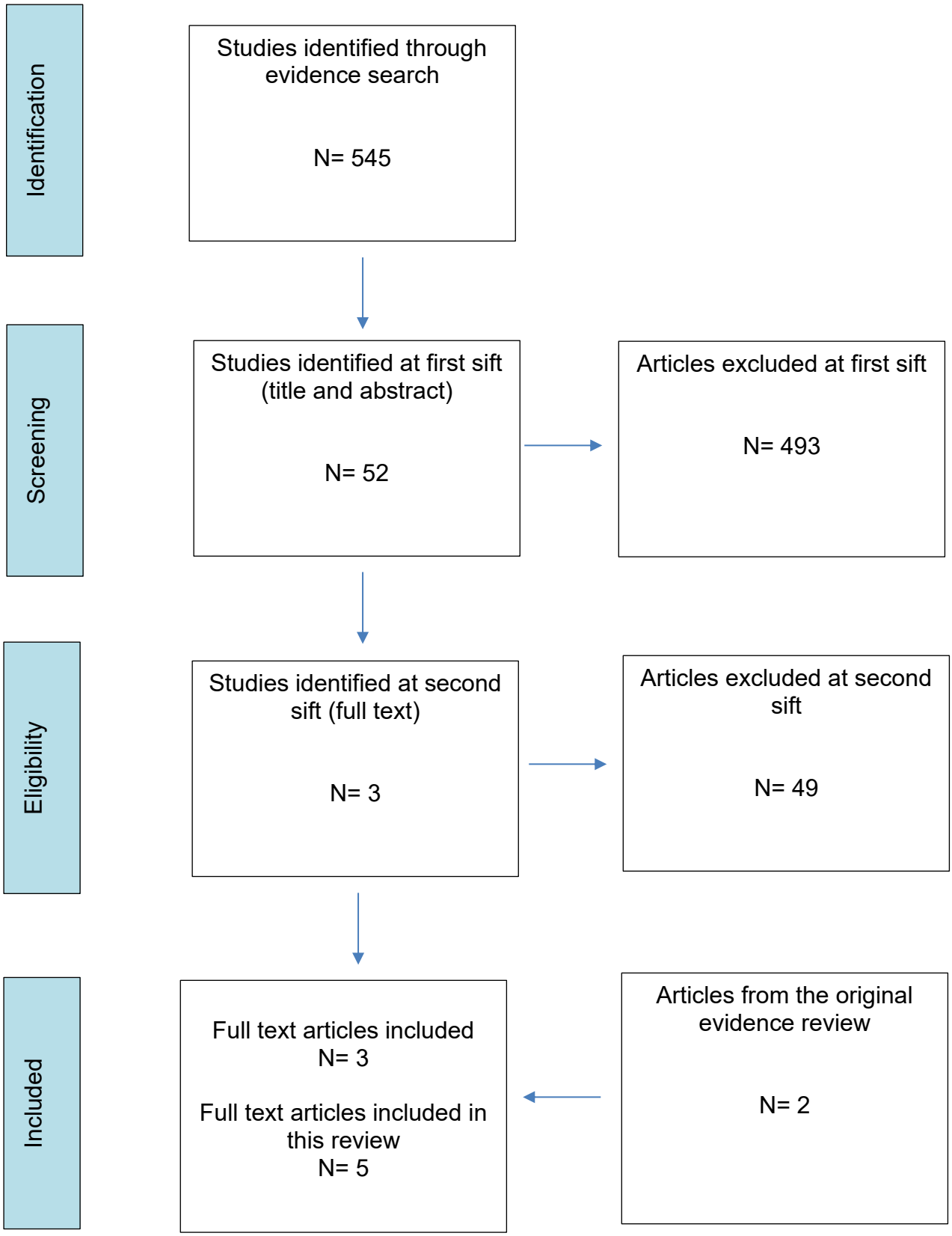
Database name: World Health Organisation Covid-19 database

tw:(tw:((tw:("non invasive" (cpap OR hfno OR bipap OR bpap))) OR (tw:("noninvasive" (cpap OR hfno OR bipap OR bpap))) OR (tw:("non invasive" "positive airway pressure")) OR (tw:("noninvasive" "positive airway pressure"))) AND (year_cluster:[2021 TO 2022])) AND type_of_study:("clinical_trials" OR "systematic_reviews") AND (year_cluster:[2021 TO 2022])

tw:((tw:("non invasive" (oxygen OR ventil* OR helmet*))) OR (tw:(non invasive (oxygen OR ventil* OR helmet*)))) AND type_of_study:("clinical_trials" OR "systematic_reviews" OR "policy_brief") AND (year_cluster:[2021 TO 2022])

tw:((tw:("high flow" (oxygen OR cannula)))) AND type:("article" OR "preprint") AND type_of_study:("clinical_trials" OR "systematic_reviews" OR "policy_brief") AND (year_cluster:[2021 TO 2022])

Appendix C: PRISMA diagram



Appendix D: Included studies

Study	Code [Reason]
Grieco, Domenico Luca, Menga, Luca S, Cesarano, Melania et al. (2021) 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	- Primary study
Menga, Luca S, Grieco, Domenico Luca, Rosa, Tommaso et al. (2021) Dyspnoea and clinical outcome in critically ill patients receiving noninvasive support for COVID-19 respiratory failure: post hoc analysis of a randomised clinical trial. ERJ open research 7(4)	- Primary study **[New study]** *Post-hoc analysis of: 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: 1731–1743.*
Nair, Parvathy Ramachandran, Haritha, Damarla, Behera, Srikant et al. (2021) Comparison of High-Flow Nasal Cannula and Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure Due to Severe COVID-19 Pneumonia. Respiratory care	- Primary study **[New study]**
Ospina-Tascon Gustavo, A, Calderon-Tapia Luis, Eduardo, Garcia Alberto, F et al. (2021) Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial. JAMA 326(21): 2161-2171	- Primary study **[New study]**
Perkins Gavin, D, Ji, Chen, Connolly Bronwen, A et al. (2022) Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA	- Primary study

Appendix E: Excluded studies at full text screening

Study reference	Reason for exclusion
Adly, Aya Sedky; Adly, Mahmoud Sedky; Adly, Afnan Sedky (2021) Telemanagement of home-isolated COVID-19 patients using oxygen therapy with noninvasive positive pressure ventilation and physical therapy techniques: Randomized clinical trial. Journal of Medical Internet Research 23(4): e23446	- Comparator in study does not match that specified in protocol
Alviset, Sophie, Riller, Quentin, Aboab, Jerome et al. Continuous positive airway pressure face-mask ventilation to manage massive influx of patients requiring respiratory support during the SARS-CoV-2 outbreak. medrxiv preprint	- Not a relevant study design
Arabi, Yaseen M, Tlayjeh, Haytham, Aldekhyl, Sara et al. (2021) Helmet Non-Invasive Ventilation for COVID-19 Patients (Helmet-COVID): study protocol for a multicentre randomised controlled trial. BMJ open 11(8): e052169	- Study protocol
Arabi, Yaseen, Tlayjeh, Haytham, Aldekhyl, Sara et al. Helmet noninvasive ventilation for COVID-19 patients (Helmet-COVID): study protocol for a multicenter randomized controlled trial. medrxiv preprint	- Not a relevant study design
Arabi, Yaseen, Tlayjeh, Haytham, Aldekhyl, Sara et al. Statistical Analysis Plan for the Helmet Non-Invasive Ventilation for COVID-19 Patients (Helmet-COVID) Randomized Controlled Trial. medrxiv preprint	- Not a relevant study design
Ari, Arzu and Moody, Gerald B. (2021) How to deliver aerosolized medications through high flow nasal cannula safely and effectively in the era of COVID-19 and beyond: A narrative review. Can J Respir Ther 57: 22-25	- Review article but not a systematic review
Ashish, Abdul, Unsworth, Alison, Martindale, Jane et al. Early CPAP reduced mortality in covid-19 patients. Audit results from Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust. medrxiv preprint	- Not a relevant study design
Boet, Sylvain, Katznelson, Rita, Castelluci Lana, A. et al. Protocol for a multicentre randomized controlled trial of normobaric versus hyperbaric oxygen therapy for hypoxemic COVID-19 patients. medrxiv preprint	- Study protocol
Boscolo, Annalisa, Pasin, Laura, Sella, Nicol? et al. (2021) Outcomes of COVID-19 patients intubated after failure of non-invasive	- Not a relevant study design

Study reference	Reason for exclusion
ventilation: a multicenter observational study. Sci Rep 11(1): 17730-17730	
Cammarota, Gianmaria, Esposito, Teresa, Azzolina, Danila et al. (2021) Noninvasive respiratory support outside the intensive care unit for acute respiratory failure related to coronavirus-19 disease: a systematic review and meta-analysis. Critical care (London, England) 25(1): 268	- This systematic review was used as a source of references
Cammarota, Gianmaria, Vaschetto, Rosanna, Azzolina, Danila et al. (2021) Early extubation with immediate non-invasive ventilation versus standard weaning in intubated patients for coronavirus disease 2019: a retrospective multicenter study. Sci Rep 11(1): 13418-13418	- Not a relevant study design
College, S. R. M. Medical and Research, Centre (2021) Comparison of effect of High Flow Nasal Cannula with Continuous Positive Airway Pressure in reducing incidence of invasive mechanical ventilation in severe COVID 19 patients.	- Not a relevant study design
Coppadoro, Andrea, Benini, Annalisa, Fruscio, Robert et al. (2021) Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak. Crit Care 25(1): 80-80	- Not a relevant study design
Culmer, Peter, Keeling, Andrew, Osnes, Cecilie et al. Delivering oxygen-enriched CPAP respiratory support using a non-invasive ventilation device. medrxiv preprint	- Not a relevant study design
Dayya, D, ONeill, OJ, Feiertag, TD et al. (2021) The use of oxygen hoods in patients failing on conventional high-flow oxygen delivery systems, the effects on oxygenation, mechanical ventilation and mortality rates in hypoxic patients with COVID-19. A Prospective Controlled Cohort Study. Respiratory medicine 179: 106312	- Not a relevant study design
Diaz De Teran, Teresa, Gonzales Martinez, Monica, Banfi, Paolo et al. (2021) Management of patients with severe acute respiratory failure due to SARS-CoV-2 pneumonia with noninvasive ventilatory support outside Intensive Care Unit. Minerva Med 112(3): 329-337	- Not a relevant study design
Dr Dy Patil Medical College, Hospital and Research, Centre (2021) CLINICAL OUTCOMES OF COVID-19 INDIAN PATIENTS	- Not a relevant study design

Study reference	Reason for exclusion
AFTER SEQUENTIAL OXYGEN THERAPY IN TERTIARY MEDICAL COLLEGE.	
Fern?ndez, R., Gonz?lez de Molina, F. J., Batlle, M. et al. (2021) Non-invasive ventilatory support in patients with COVID-19 pneumonia: A Spanish multicenter registry. Med Intensiva (Engl Ed) 45(5): 315-317	- Not a relevant study design
Forrest, Iain S, Jaladanki, Suraj K, Paranjpe, Ishan et al. (2021) Non-invasive ventilation versus mechanical ventilation in hypoxemic patients with COVID-19. Infection 49(5): 989-997	- Comparator in study does not match that specified in protocol
George Institute for Global Health, India (2021) PROVE Trial - Positive pRessure therapy in COVid-19 infEction.	- Not a relevant study design
Germans Trias i Pujol, Hospital (2021) Predictors of Non-invasive Respiratory Support Failure in COVID-19 Pneumonia.	- Not a relevant study design
Ghani, Hakim, Shaw, Michael, Pyae, Phyoe et al. Evaluation of the ROX index in SARS-CoV-2 Acute Respiratory failure treated with both High-Flow Nasal Oxygen (HFNO) and Continuous Positive Airway Pressure (CPAP). medrxiv preprint	- Not a relevant study design
Gidaro, Antonio, Samartin, Federica, Brambilla Anna, Maria et al. Occurrence of Pneumothorax and Pneumomediastinum in Covid-19 patients during non-invasive ventilation with Continuous Positive Airway Pressure. medrxiv preprint	- Not a relevant study design
Goh, QY, Lie, SA, Tan, Z et al. (2021) Time to intubation with McGrath™ videolaryngoscope versus direct laryngoscope in powered air-purifying respirator: a randomised controlled trial. Singapore medical journal	- Study does not contain a relevant intervention
Gorman, Ellen, Connolly, Bronwen, Couper, Keith et al. (2021) Non-invasive respiratory support strategies in COVID-19. The Lancet. Respiratory medicine 9(6): 553-556	- Not a relevant study design
Gough, Ciara, Casey, Michelle, McCartan, Thomas A. et al. (2021) Effects of non-invasive respiratory support on gas exchange and outcomes in COVID-19 outside the ICU. Respir Med 185: 106481-106481	- Not a relevant study design
Government Institute of Medical, Sciences (2021) Non Invasive Ventilation by Helmet mask vs. Facemask in Covid pneumonia patients.	- Not a relevant study design

Study reference	Reason for exclusion
Grosgurin, Olivier, Leidi, Antonio, Farhoumand Pauline, Darbellay-Farhoumand et al. Role of intermediate care unit admission and non-invasive respiratory support during the COVID-19 pandemic: a retrospective cohort study. medrxiv preprint	- Not a relevant study design
Junhai, Zhen Jing Yan Beibei Cao Li Li (2021) The Value of ROX Index in Predicting the Outcome of High Flow Nasal Cannula: A Systematic Review and Meta-analysis.	- Not a relevant study design
Khatib, MY, Peediyakkal, MZ, Elshafei, MS et al. (2021) Comparison of the clinical outcomes of noninvasive ventilation by helmet vs facemask in patients with acute respiratory distress syndrome. Medicine (united states) 100(4)	- Not a relevant study design
Kumar, A, Sinha, C, Kumar, A et al. (2021) Low flow nasal oxygen supplementation in addition to non-rebreathing mask: an alternative to high flow nasal cannula oxygenation for acute hypoxemic COVID-19 patients in resource limited settings. Trends in anaesthesia and critical care	- Not a relevant study design
Lee, Sarah, Bradley, W. Pierre L., Brewster, David J. et al. (2021) Airway management in the adult patient with COVID-19: High flow nasal oxygen or not? A summary of evidence and local expert opinion. Anaesth Intensive Care 49(4): 268-274	- Review article but not a systematic review
Lewis, Sharon R., Baker, Philip E., Parker, Roses et al. (2021) High-flow nasal cannulae for respiratory support in adult intensive care patients. Cochrane Database Syst Rev 3: cd010172-cd010172	- This systematic review was used as a source of references
Liu, Ling, Xie, Jianfeng, Wu, Wenjuan et al. (2021) A simple nomogram for predicting failure of non-invasive respiratory strategies in adults with COVID-19: a retrospective multicentre study. Lancet Digit Health 3(3): e166-e174	- Not a relevant study design
Mellado-Artigas, Ricard, Ferreyro, Bruno L., Angriman, Federico et al. (2021) High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. Crit Care 25(1): 58-58	- Not a relevant study design
Menga, Luca S, Berardi, Cecilia, Ruggiero, Ersilia et al. (2022) Noninvasive respiratory support for acute respiratory failure due to COVID-19. Current opinion in critical care 28(1): 25-50	- Review article but not a systematic review

Study reference	Reason for exclusion
Mohammadi, Mostafa; Khamseh Alireza Khafaee, Pour; Varpaei Hesam, Aldin Invasive airway "Intubation" in COVID-19 patients: statistics, causes and recommendations. medrxiv preprint	- Not a relevant study design
Noto, Alberto, Crimi, Claudia, Cortegiani, Andrea et al. Performance of EasyBreath(R) Decathlon Snorkeling mask for Delivering Continuous Positive Airway Pressure. medrxiv preprint	- Not a relevant study design
Ogawa, Kenta, Asano, Kengo, Ikeda, Junpei et al. (2021) Non-invasive oxygenation strategies for respiratory failure with COVID-19: A concise narrative review of literature in pre and mid-COVID-19 era. Anaesthesia, critical care & pain medicine 40(4): 100897	- Review article but not a systematic review
Pearson, S. D., Stutz, M. R., Lecompte-Osorio, P. et al. (2021) Helmet noninvasive ventilation versus high flow nasal cannula for COVID-19 related acute hypoxemic respiratory failure. American Journal of Respiratory and Critical Care Medicine 203(9)	- Not a relevant study design
Radovanovic, Dejan, Santus, Pierachille, Coppola, Silvia et al. (2021) Characteristics, outcomes and global trends of respiratory support in patients hospitalized with COVID-19 pneumonia: a scoping review. Minerva anestesiologica 87(8): 915-926	- Review article but not a systematic review
Rasmussen, Bodil S, Klitgaard, Thomas L, Perner, Anders et al. (2022) Oxygenation targets in ICU patients with COVID-19: A post hoc subgroup analysis of the HOT-ICU trial. Acta anaesthesiologica Scandinavica 66(1): 76-84	- Study does not contain a relevant intervention
Russell, B., Ralston, S. L., Compton, B. et al. (2021) Impact of low flow nasal cannula failure criteria on high flownasal cannula utilization: A quality improvement project. Pediatrics 147(3): 569-570	- Not a relevant study design
Sutradhar, D. R. Saurav (2021) A multicentre observational study to look into the practise of using non invasive ventilation in COVID-19 patients requiring ICU admission for respiratory support and their outcome in terms of their failure rate as well as exploiting the HACOR scale to predict NiV failure.	- Not a relevant study design
Szakmany, Tamas (2020) noninvasive ventilatory support in coviD-19: Operating in the evidence free zone. Minerva Anestesiologica 86(11): 1126-1128	- Not a relevant study design

Study reference	Reason for exclusion
Teng, Xiao-Bao, Shen, Ya, Han, Ming-Feng et al. (2020) The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. European journal of clinical investigation: e13435	Incorrect study type (not an RCT)
Wang, Zhufeng, Wang, Yingzhi, Yang, Zhaowei et al. (2021) The use of non-invasive ventilation in COVID-19: A systematic review. Int J Infect Dis 106: 254-261	- This systematic review was used as a source of references
Weerakkody, Sampath, Arina, Pietro, Glenister, James et al. (2021) Non-invasive respiratory support in the management of acute COVID-19 pneumonia: considerations for clinical practice and priorities for research. The Lancet. Respiratory medicine	- Review article but not a systematic review

Appendix F: Evidence tables

Grieco, 2021

Bibliographic Reference	Grieco, Domenico Luca; Menga, Luca S; Cesarano, Melania; Rosa, Tommaso; Spadaro, Savino; Bitondo, Maria Maddalena; Montomoli, Jonathan; Falo, Giulia; Tonetti, Tommaso; Cutuli, Salvatore L; Pintaudi, Gabriele; Tanzarella, Eloisa S; Piervincenzi, Edoardo; Bongiovanni, Filippo; Dell'Anna, Antonio M; Delle Cese, Luca; Berardi, Cecilia; Carelli, Simone; Bocci, Maria Grazia; Montini, Luca; Bello, Giuseppe; Natalini, Daniele; De Pascale, Gennaro; Velardo, Matteo; Volta, Carlo Alberto; Ranieri, V Marco; Conti, Giorgio; Maggiore, Salvatore Maurizio; Antonelli, Massimo; COVID-ICU Gemelli Study, Group; 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

Study details

Trial registration (if reported)	NCT04502576
Study start date	13-Oct-2020
Study end date	13-Dec-2020
Aim of the study	To assess whether helmet noninvasive ventilation can increase the days free of respiratory support in patients with COVID-19 compared with high-flow nasal oxygen alone.
Country/geographical location	Italy.
Population description	109 patients with COVID-19 and moderate to severe hypoxemic respiratory failure (ratio of partial pressure of arterial oxygen to fraction of inspired oxygen equal to or below 200).
Inclusion criteria	Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) equal to or below 200, partial pressure of arterial carbon dioxide (PaCO2) equal to or lower than 45 mm Hg, absence of history of chronic respiratory failure or moderate to severe cardiac insufficiency (New York Heart Association class >II or left ventricular ejection fraction <50%), confirmed molecular diagnosis of COVID-19, and written informed consent.
Exclusion criteria	Acute exacerbation of chronic pulmonary disease and kidney failure were the main exclusion criteria. Patients who had already received noninvasive ventilation or high-flow oxygen for more than 12 hours at the time of screening were also excluded.
Intervention dosage (loading)	Helmet noninvasive ventilation (positive end-expiratory pressure, 10-12 cm H2O; pressure support, 10-12 cm H2O).

Intervention scheduled duration	At least 48 hours. Treatment was continued until the patient required endotracheal intubation or (in case of no intubation) up to intensive care unit discharge.
Intervention actual duration	Helmet noninvasive ventilation was delivered continuously in the first 48 hours or until intubation in 49 patients (91%); 2 patients (4%) did not undergo continuous treatments but received helmet noninvasive ventilation for at least 16 hours in each of the first 2 days. Two patients (4%) could not tolerate the interface and interrupted noninvasive ventilation without receiving 16 hours per day of treatment. One patient did not receive noninvasive ventilation despite assignment to this group.
Intervention route of administration	Helmet ventilation apparatus.
Comparator (where applicable)	High-flow oxygen alone (60 L/min) delivered continuously for 48 hours or until intubation.
Methods for population selection/allocation	All consecutive adult patients diagnosed with COVID-19 admitted in the intensive care units due to acute hypoxemic respiratory failure were screened for enrolment. Eligibility inclusion criteria were assessed within the first 24 hours from intensive care unit admission, while patients were receiving oxygen through a Venturi mask, with nominal fraction of inspired oxygen (FIO2) ranging between 24% and 60% as set by the attending physician. Enrolled patients were randomized in a 1:1 ratio to receive either helmet noninvasive ventilation or high-flow nasal oxygen. 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.
Methods of data analysis	Data were tabulated descriptively by study group and analysed for all randomized patients in the primary analysis.
Attrition/loss to follow-up	110 were eligible for inclusion in the study and underwent randomization. Fifty five patients were assigned to each group. After secondary exclusion of 1 patient who had a newly diagnosed end-stage pulmonary fibrosis with do-not-intubate order, 109 patients were included in the follow-up and in the primary analysis. Two patients showed major protocol violations: 1 patient received noninvasive ventilation despite being assigned to the high-flow nasal oxygen group, and 1 patient did not receive helmet noninvasive ventilation because of ventilator unavailability; 107 patients were included in the prespecified secondary analysis on patients who did not show protocol violations.
Source of funding	The study was funded by a research grant (2017 Merck Sharp & Dohme SRL award) by the Italian Society of Anesthesia, Analgesia, and Intensive Care Medicine.
Study limitations (Author)	The limited sample could have made the study underpowered to detect small differences between groups in the primary end point. Second, helmet noninvasive ventilation was applied continuously for at least 48 hours with high positive end-expiratory pressure and relatively low pressure support in centres with expertise with this technique. Use of this technique with different ventilator settings, with non adequate personnel expertise, and/or in intermittent sessions may not provide the same benefits observed in our study.

	Third, the use of awake prone positioning was not standardized and occurred more frequently in patients in the high-flow nasal oxygen group, as per clinical decision: this does not alter, and could even strengthen, the significance of the results on endotracheal intubation because prone positioning could have optimized the perceived benefit by high flow oxygen. Fourth, all enrolled patients were affected by COVID-19, and the results, despite being physiologically sound and consistent with the most recent literature on acute hypoxemic respiratory of other ethnologies, may not fully be generalizable to hypoxemic respiratory failure due to other causes.
Other details	Outcome data on dyspnoea in critically ill patients receiving noninvasive support for COVID-19 respiratory failure is from a *post hoc* analysis. Dyspnoea and clinical outcome in critically ill patients receiving noninvasive support for COVID-19 respiratory failure: *post hoc* analysis of a randomised clinical trial Luca S. Menga, Domenico Luca Grieco, Tommaso Rosà, Melania Cesarano, Luca Delle Cese, Cecilia Berardi, Gabriele Pintaudi, Eloisa Sofia Tanzarella, Salvatore L. Cutuli, Gennaro De Pascale, Salvatore Maurizio Maggiore, Massimo Antonelli for the COVID-ICU Gemelli study group ERJ Open Research 2021 7: 00418-2021; **DOI:** 10.1183/23120541.00418-2021

Study arms

Helmet noninvasive ventilation followed by high-flow nasal oxygen (N = 54)
Continuous treatment with helmet non-invasive ventilation (positive end-expiratory pressure, 10-12 cm H2O; pressure support, 10-12 cm H2O) for at least 48 hours eventually followed by high-flow nasal oxygen

High-flow oxygen alone (N = 55)

Characteristics

Arm-level characteristics

Characteristic	Helmet noninvasive ventilation followed by high-flow nasal oxygen (N = 54)	High-flow oxygen alone (N = 55)
Age Median (IQR)	66 (57 to 72)	63 (55 to 69)
Female No of events	n = 12 ; % = 22	n = 9 ; % = 16
Male No of events	n = 42 ; % = 77	n = 46 ; % = 84

Characteristic	Helmet noninvasive ventilation followed by high-flow nasal oxygen (N = 54)	High-flow oxygen alone (N = 55)
Hypertension No of events	n = 24 ; % = 44	n = 33 ; % = 60
Type 2 diabetes No of events	n = 13 ; % = 24	n = 10 ; % = 18
Smoking No of events	n = 5 ; % = 9	n = 11 ; % = 20
Immunocompromised state No of events	n = 3 ; % = 6	n = 5 ; % = 9
Recent chemotherapy No of events	n = 2 ; % = 4	n = 0 ; % = 0
HIV No of events	n = 1 ; % = 2	n = 1 ; % = 2
Immunosuppressor therapy-kidney transplant No of events	n = 0 ; % = 0	n = 2 ; % = 4
Acute myeloid leukaemia No of events	n = 0 ; % = 0	n = 1 ; % = 2
Ulcerative colitis-immunosuppressor therapy No of events	n = 0 ; % = 0	n = 1 ; % = 2
History of cancer No of events	n = 4 ; % = 8	n = 0 ; % = 0
Neurologic conditions No of events	n = 0 ; % = 0	n = 2 ; % = 4
Autism spectrum disorders No of events	n = 0 ; % = 0	n = 1 ; % = 2
Alzheimer's disease No of events	n = 0 ; % = 0	n = 1 ; % = 2

Outcomes

Primary and secondary outcomes

Outcome	Helmet noninvasive ventilation followed by high-flow nasal oxygen, , N = 54	High-flow oxygen alone, , N = 55
Respiratory support–free days, median (IQR) Nominal	20	18
Respiratory support–free days, median (IQR) Range	0 to 25	0 to 22
Intubation within 28 d from enrolment No of events	n = 16 ; % = 30	n = 28 ; % = 51
Intubation within 28 d from enrolment after adjudication of intubation criteria by external experts No of events	n = 15 ; % = 28	n = 28 ; % = 51
28 d Nominal	28	25
28 d Range	13 to 28	4 to 28
60 d Nominal	60	57
60 d Range	43 to 60	19 to 60
In–intensive care unit mortality No of events	n = 11 ; % = 20	n = 14 ; % = 25
In-hospital mortality No of events	n = 13 ; % = 24	n = 14 ; % = 25
ICU Nominal	9	10
ICU Range	4 to 17	5 to 23
Hospital	21	22

Outcome	Helmet noninvasive ventilation followed by high-flow nasal oxygen, , N = 54	High-flow oxygen alone, , N = 55
Nominal		
Hospital Range	14 to 30	13 to 44
28 d No of events	n = 8 ; % = 15	n = 10 ; % = 18
60 d No of events	n = 13 ; % = 24	n = 12 ; % = 22
Moderate-to-severe dyspnoea (Menga, 2021) No of events	n = 27 % = 47	n = 25 ; % = 48
Mild or no dyspnoea (Menga, 2021) No of events	n = 27 ; % = 47	n = 30 ; % = 53

Menga, 2021 (A post hoc analysis of Grieco, 2021)

Bibliographic Reference	Menga, Luca S; Grieco, Domenico Luca; Rosa, Tommaso; Cesarano, Melania; Delle Cese, Luca; Berardi, Cecilia; Pintaudi, Gabriele; Tanzarella, Eloisa Sofia; Cutuli, Salvatore L; De Pascale, Gennaro; Maggiore, Salvatore Maurizio; Antonelli, Massimo; Dyspnoea and clinical outcome in critically ill patients receiving noninvasive support for COVID-19 respiratory failure: post hoc analysis of a randomised clinical trial.; ERJ open research; 2021; vol. 7 (no. 4)

Study details

Trial registration (if reported)	ClinicalTrials.gov Identifier: NCT04502576
Study start date	13-Oct-2020
Study end date	11-Feb-2021
Aim of the study	To assess the prevalence of dyspnoea in COVID-19 patients admitted to the intensive care unit (ICU) and to determine whether this may be related to study outcomes. Study outcomes: To assess whether helmet noninvasive ventilation can increase the days free of respiratory support in patients with COVID-19 compared with high-flow nasal oxygen alone.

Country/geographical location	Dimar, Italy, or Starmed-Intersurgical, UK
Population description	109 patients admitted to four ICUs and receiving noninvasive respiratory support due to COVID-19 acute hypoxaemic respiratory failure (arterial oxygen tension (*P*aO2)/inspiratory oxygen fraction (*F*IO2) ratio ≤200)
Inclusion criteria	Adults (18 years and over). Acute-onset respiratory distress or flue-related symptoms Moderate-to-severe hypoxemia (PaO2/FiO2<=200 mmHg) PaCO2<45 mmHg pH>7.30
Exclusion criteria	Need for urgent endo-tracheal intubation Exacerbation of asthma or chronic obstructive pulmonary disease Documented pneumothorax Clinical diagnosis of Cardiogenic pulmonary oedema Do-not-intubate order Altered neurological status that requires immediate intubation and/or making the patient uncooperative Thoracic or abdominal surgery in the previous 7 days Recent head surgery or anatomy that prevent the application of helmet or Optiflow to patient's face
Intervention dosage (loading)	Helmet noninvasive ventilation (positive end-expiratory pressure, 10-12 cm H2O; pressure support, 10-12 cm H2O).
Intervention scheduled duration	At least 48 hours. Treatment was continued until the patient required endotracheal intubation or (in case of no intubation) up to intensive care unit discharge.
Intervention actual duration	Helmet noninvasive ventilation was delivered continuously in the first 48 hours or until intubation in 49 patients (91%); 2 patients (4%) did not undergo continuous treatments but received helmet noninvasive ventilation for at least 16 hours in each of the first 2 days. Two patients (4%) could not tolerate the interface and interrupted noninvasive ventilation without receiving 16 hours per day of treatment. One patient did not receive noninvasive ventilation despite assignment to this group
Intervention route of administration	Helmet ventilation apparatus.
Comparator (where applicable)	High-flow oxygen alone (60 L/min) delivered continuously for 48 hours or until intubation.
Methods of data analysis	Post hoc analysis of Grieco (2021)

Study arms
Helmet NIV (N = 54)
Continuous treatment with helmet NIV

High-flow oxygen alone (N = 55)

For characteristics and outcomes please see Grieco et al. (2021) above.

Nair, 2021

Bibliographic Reference	Nair, Parvathy Ramachandran; Haritha, Damarla; Behera, Srikant; Kayina, Choro Athiphro; Maitra, Souvik; Anand, Rahul Kumar; Ray, Bikash Ranjan; Soneja, Manish; Subramaniam, Rajeshwari; Baidya, Dalim Kumar; Comparison of High-Flow Nasal Cannula and Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure Due to Severe COVID-19 Pneumonia.; Respiratory care; 2021

Study details

Trial registration (if reported)	The study was registered at the Clinical Trials Registry of India (www.ctri.nic.in; reference number: CTRI/2020/07/026835) on July 27, 2020.
Study start date	Aug-2020
Study end date	Dec-2020
Aim of the study	Aimed to assess the incidence of invasive mechanical ventilation in patients with acute hypoxemic respiratory failure due to COVID-19 treated with either HFNC or NIV
Country/geographical location	ICU of a tertiary care teaching hospital in New Delhi, India
Population description	One hundred and nine subjects with severe COVID-19 pneumonia presenting with acute hypoxemic respiratory failure.
Inclusion criteria	Subjects with laboratory-confirmed diagnosis of COVID-19 pneumonia, presenting with severe COVID-19 pneumonia, who failed oxygen therapy by face mask, were included in this study after obtaining informed written consent from the subjects or their legally acceptable representatives. Adult subjects of age 18–75 y were considered, and the following definitions were followed: - Severe COVID-19 pneumonia: Subjects presenting with fever, cough, and respiratory distress with frequency > 30 breaths/min and/or room air SpO2 < 90%. - Failure of oxygen therapy by face mask: Subjects with frequency > 24 breaths/min and/or SpO2 < 94% in spite of oxygen by face mask at 10 L/min flow for 30 min
Exclusion criteria	Exclusion criteria: Hemodynamic instability and requirement of high-dose vasopressor therapy; pregnancy; COPD/chronic respiratory failure; morbid obesity; patients with urgent requirement of invasive mechanical ventilation, severe hypoxia (SpO2 < 90% with frequency > 40 breaths/min for > 10 min), severe hemodynamic instability (mean arterial pressure < 65 mm Hg in spite of high-dose noradrenaline support) with altered mentation, Glasgow coma scale score < 8, or cardiac arrest were excluded.
Intervention dosage (loading)	HFNC arm: The initial gas flow was set at 50 L/min and FIO2 of 1.0. NIV arm: ICU ventilator with the setting of pressure support (PS) of 10–20 cm H2O adjusted with the aim of obtaining an expired tidal volume of 7–10 mL per kilogram of predicted body weight and

	PEEP 5–10 cm H2O and FIO2 0.5–1.0 titrated to target SpO2 > 94%.
Intervention dosage (maintenance)	HFNC arm: The flow and FIO2 were subsequently adjusted between 30–60 L/min and 0.5–1.0, respectively, to maintain SpO2 of 94% or more.
Intervention scheduled duration	Up to 28 days
Intervention actual duration	Up to 28 days
Intervention route of administration	HFNC arm: Subjects received HFNC through large-bore binasal prongs with a high-flow heated humidifier device (Optiflow, Fisher & Paykel Healthcare, Auckland, New Zealand). NIV arm: Subjects allocated to NIV arm were applied to NIV with either mask/helmet device connected to an ICU ventilator
Comparator (where applicable)	Other clinical management: Clinical management of all subjects including fluid therapy, monitoring of vitals, baseline blood investigations, chest radiograph, and point-of care ultrasound was as per standard institute protocol. All subjects received supportive drug therapy as per current institutional protocol. Awake prone positioning was encouraged to subjects and allowed at the discretion of attending ICU physician
Methods for population selection/allocation	Convenience sample size of around 100 subjects. Eligible subjects were randomized with a computer-generated random number table (www.randomizer.org) in to either group A (HFNC) or group B (NIV) according to a computer-generated random number table. Allocation concealment was done with sealed-envelope technique. The ICU doctor informed the subjects about group allocation, obtained consent, noted the baseline data, and initiated the intervention. The subject and the clinical management team were not blinded to the allocated intervention. However, an independent investigator unaware of the group allocation noted the outcome variables after 48 h of randomization and thereafter from the subjects' database and files.
Methods of data analysis	Data were presented as median and interquartile range (IQR) for continuous variables and as absolute numbers or percentages for categorical variables. Unrelated data were compared by Mann-Whitney U test or chi-square test as applicable. Risk ratio and 95% CI were estimated by generalized linear modelling of binomial family. Correlated variables were compared by paired sample t test or Wilcoxon matched-pairs test. A 2-sided P value < .05 was considered as significant. Probability of death during hospital stay was evaluated by Kaplan-Meier survival analysis, and hazard ratio (HR) with 95% CI was reported. Baseline imbalance between the 2 study groups was adjusted individually by binary logistic regression model, and adjusted odds ratio for individual unbalanced parameters was reported.

Attrition/loss to follow-up	145 patients were assessed for eligibility. Thirty six patients were ineligible for the study as they either met the criteria for intubation or declined to participate. Out of the 109 subjects who underwent randomization, 55 were assigned to the HFNC group and 54 to the NIV group.
Source of funding	Not stated
Study limitations (Author)	We understand that there are multiple limitations of this study. This is a single-center trial, and blinding of primary caregiver was not possible due to obvious reasons. We could not report the proportion of subjects performing awake prone sessions. Although all the subjects were encouraged for awake prone sessions, frequent self-changing of positions by subjects in HFNC group and noncompliance in NIV group did not allow proper data keeping. We calculated sample size on the basis of 30% reduction in endotracheal intubation rate, but it was not achieved; hence, our study was actually underpowered to detect such actual difference in the primary outcome.
Other details	Other clinical management: Clinical management of all subjects including fluid therapy, monitoring of vitals, baseline blood investigations, chest radiograph, and point-of-care ultrasound was as per standard institute protocol. All subjects received supportive drug therapy as per current institutional protocol. Awake prone positioning was encouraged to subjects and allowed at the discretion of attending ICU physician

Study arms
High-flow nasal cannula (HFNC) (N = 55)

Noninvasive ventilation (NIV) (N = 54)

Characteristics
Arm-level characteristics

Characteristic	High-flow nasal cannula (HFNC) (N = 55)	Noninvasive ventilation (NIV) (N = 54)
Age Median (IQR)	57 (48 to 65)	57.5 (47 to 64)
Gender (n (%)) Male No of events	n = 44 ; % = 80	n = 35 ; % = 64.8
Diabetes mellitus No of events	n = 17 ; % = 30.9	n = 16 ; % = 29.62
Hypertension No of events	n = 17 ; % = 30.9	n = 20 ; % = 37.03

Characteristic	High-flow nasal cannula (HFNC) (N = 55)	Noninvasive ventilation (NIV) (N = 54)
Chronic kidney disease No of events	n = 4 ; % = 7.27	n = 12 ; % = 22.22
Chronic liver disease No of events	n = 1 ; % = 1.81	n = 1 ; % = 1.85
Coronary artery disease No of events	n = 10 ; % = 18.18	n = 7 ; % = 12.96

Outcomes

Primary and secondary outcomes

Outcome	High-flow nasal cannula (HFNC), , N = 55	Noninvasive ventilation (NIV), , N = 54
Intubation within 48h No of events	n = 11 ; % = 20	n = 18 ; % = 33.3
Intubation within 7 day No of events	n = 15 ; % = 27.3	n = 25 ; % = 46.3
Mortality No of events	n = 16 ; % = 29.1	n = 25 ; % = 46.3
Ventilator-free days at day 28 Median (IQR)	28 (27 to 28)	27.5 (27 to 28)
Hospital length of stay, day Median (IQR)	9 (7 to 13)	9 (6 to 12)
Frequency, breaths/min Median (IQR)	25 (22 to 27)	26 (22 to 30)
SpO2 % Median (IQR)	96 (93 to 98)	96 (94 to 98)
PaO2 /FIO2 Median (IQR)	113 (90.1 to 181.7)	124.4 (90.87 to 179)
Frequency, breaths/min	24 (20 to 28)	24 (21 to 28)

Outcome	High-flow nasal cannula (HFNC), , N = 55	Noninvasive ventilation (NIV), , N = 54
Median (IQR)		
SpO2 % Median (IQR)	96 (93 to 98)	96 (93 to 98)
PaO2 /FIO2 Median (IQR)	118.33 (89.8 to 193.3)	153.6 (105 to 213.5)

Ospina-Tascon Gustavo, 2021

Bibliographic Reference	Ospina-Tascon Gustavo, A; Calderon-Tapia Luis, Eduardo; Garcia Alberto, F; Zarama, Virginia; Gomez-Alvarez, Freddy; Alvarez-Saa, Tatiana; Pardo-Otalvaro, Stephania; Bautista-Rincon Diego, F; Vargas Monica, P; Aldana-Diaz Jose, L; Marulanda, Angela; Gutierrez, Alejandro; Varon, Janer; Gomez, Monica; Ochoa Maria, E; Escobar, Elena; Umana, Mauricio; Diez, Julio; Tobon Gabriel, J; Albornoz Ludwig, L; Celemin, Florez; Carlos, Augusto; Ruiz Guillermo, Ortiz; Caceres Eder, Leonardo; Reyes Luis, Felipe; Damiani Lucas, Petri; Cavalcanti Alexandre, B; HiFLo-Covid, Investigators; Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial.; JAMA; 2021; vol. 326 (no. 21); 2161-2171

Study details

Trial registration (if reported)	ClinicalTrials.gov Identifier: NCT04609462
Study start date	01-Aug-2020
Study end date	10-Feb-2021
Aim of the study	To determine the effect of high-flow oxygen therapy through a nasal cannula compared with conventional oxygen therapy on need for endotracheal intubation and clinical recovery in severe COVID-19. The co–primary outcomes were need for intubation and time to clinical recovery until day 28 as assessed by a 7-category ordinal scale (range, 1-7, with higher scores indicating a worse condition).
Country/geographical location	Colombia
Population description	A total of 220 adults with respiratory distress and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of less than 200 due to COVID-19.
Inclusion criteria	Adult patients admitted to the emergency department, general ward, or intensive care unit were enrolled if they met all of the following eligibility criteria: aged 18 years or older; suspected or

	confirmed infection with SARS-CoV-2 (confirmation via reverse transcriptase–polymerase chain reaction test from a nasopharyngeal swab); acute respiratory failure with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) of less than 200, accompanied by clinical signs of respiratory distress (e.g. use of accessory muscles and respiratory rate greater than 25/min); and less than 6 hours elapsed since fulfilling the criteria of acute respiratory failure.
Exclusion criteria	Exclusion criteria were need for immediate endotracheal intubation; a partial pressure of arterial carbon dioxide greater than 55 mm Hg; pregnancy; high suspicion or confirmation of acute cardiogenic pulmonary oedema; history of or current left ventricular ejection fraction of less than 45%; history of chronic heart failure (New York Heart Association class III-IV)16; clinical suspicion or confirmation of peripheral demyelinating disease; history of advanced chronic obstructive pulmonary disease (Global Initiative for ChronObstructive Lung Disease grade C-D)17 or hospitalization due to chronic obstructive pulmonary disease decompensation within the last year; advanced liver cirrhosis (Child-Pugh class C)18; anatomical or other conditions precluding the use of a high-flow nasal cannula; do-not-intubate or do-not resuscitate orders; imminent death; and refusal of study participation by a patient or their next of kin.
Intervention dosage (loading)	In the high-flow oxygen therapy group, respiratory support was continuously applied at an initial flow of 60 L/min and an FIO2 of 1.0.
Intervention dosage (maintenance)	In the high-flow oxygen therapy group, The FIO2 was subsequently adjusted to maintain pulse oxygen saturation (SpO2) values of 92% or greater. Flow rate was decreased in patients reporting discomfort due to high-flow oxygen therapy until its resolution. The high-flow oxygen therapy was continuously applied until intubation or when criteria for weaning of high flow oxygen therapy were achieved, namely, improvement in clinical signs of respiratory distress, a PaO2/FIO2 ratio higher than 200, and ability to maintain SpO2values of 92% or greater with less than 9 L/min of conventional oxygen therapy.
Intervention scheduled duration	Treatments were scheduled to be delivered within 30minutes until intubation or when criteria for weaning of high flow oxygen therapy were achieved (for 28 days).
Intervention actual duration	All participants were evaluated daily from day 1 through day 28 (while remaining hospitalized) by the local study coordinators and research assistants. When hospital discharge happened before day 28, patients or family representatives were contacted via a structured telephone call to verify vital and clinical status at day 28. Patients experiencing hypoxemia after weaning from high-flow oxygen therapy recommenced high-flow oxygen therapy with a nasal cannula unless immediate intubation was necessary.

Intervention route of administration	Respiratory support was continuously applied through large-bore binasal prongs using heated and humidified gas.
Comparator (where applicable)	Conventional oxygen therapy. Oxygen was applied continuously through any low-flow oxygen device or combination thereof (nasal prongs, mask with or without oxygen reservoir, Venturimask systems). Rates of gas flow and FIO2 were adjusted to maintain SpO2 values of 92% or greater until patient intubation or recovery.
Methods for population selection/allocation	Eligible patients were randomly assigned in a 1:1 ratio to receive respiratory support with high-flow oxygen therapy through a nasal cannula vs conventional oxygen therapy. Randomization was centrally performed through a web-based system using computer-generated random numbers with blocks of 2 and 4, unknown to the investigators, and was stratified by study site to ensure allocation concealment. Site investigators were unaware of block size. Baseline was defined as the time of randomization.
Methods of data analysis	Effects of treatments were calculated with a Cox proportional hazards model adjusted for hypoxemia severity, age, and comorbidities.
Attrition/loss to follow-up	Started at 220 participants. There was a loss of 21 participants: High-flow oxygen therapy (n = 99) Conventional oxygen therapy (n = 100)
Source of funding	This study received funds and logistic support from the Centro de Investigaciones Clínicas, Fundación Valle del Lili, Cali, Colombia.
Study limitations (Author)	This study has several limitations. First, because of its nature, this open-label trial lacked the possibility of blinding, which may affect the assessment of outcomes. Second, all participants were recruited in only 3 centers from 1 country, which restricts the generalizability of the results. Third, the trial design considered 2 co–primary end points, raising the potential for type I error. Fourth, analysis of secondary outcomes was not adjusted by multiplicity; these results should be considered exploratory. Fifth, the sample size of this trial and the number of events were relatively small, and therefore small variations in the number of events would have rendered treatment effect on the co–primary outcomes nonsignificant. Sixth, measurements or estimations for the metabolic work of breathing, transpulmonary pressures, minute volume, or estimations of nonhomogeneous distribution of tidal ventilation were not performed; thus, potential mechanisms mediating the effect of high-flow oxygen therapy through a nasal cannula on the co–primary outcomes remain theoretical. Seventh, this trial was not powered to demonstrate differences in mortality; nevertheless, the effect of high-flow oxygen therapy on need for intubation and clinical recovery could encourage its use

Study arms
High-flow oxygen therapy (N = 99)
high-flow oxygen through a nasal cannula

Conventional oxygen therapy (N = 100)

Characteristics

Arm-level characteristics

Characteristic	High-flow oxygen therapy (N = 99)	Conventional oxygen therapy (N = 100)
Age Median (IQR)	60 (50 to 69)	59 (49 to 67)
Female No of events	n = 28 ; % = 28	n = 37 ; % = 37
Male No of events	n = 71 ; % = 72	n = 63 ; % = 63
Hypertension No of events	n = 35 ; % = 35	n = 44 ; % = 44
Diabetes No of events	n = 18 ; % = 18	n = 20 ; % = 20
Liver cirrhosis (Child-Pugh class A-B)f No of events	n = 35 ; % = 35	n = 44 ; % = 44
Chronic obstructive pulmonary disease No of events	n = 3 ; % = 3	n = 1 ; % = 1
Chronic heart failure No of events	n = 3 ; % = 3	n = 4 ; % = 4
Chronic kidney disease No of events	n = 0 ; % = 0	n = 1 ; % = 1
Cancer No of events	n = 1 ; % = 1	n = 0 ; % = 0
Body mass index, median (IQR)d Median (IQR)	28.7 (26.3 to 32.1)	29.4 (26.2 to 33.1)

Outcomes

Primary and secondary outcomes

Outcome	High-flow oxygen therapy, , N = 99	Conventional oxygen therapy, , N = 100
Intubation within 28 d, No. (%) No of events	n = 34 ; % = 34.3	n = 51 ; % = 51
Clinical recovery within 28 d, No. (%) No of events	n = 77 ; % = 77.8	n = 71 ; % = 71
Time to clinical recovery, median (IQR) Median (IQR)	11 (9 to 14)	14 (11 to 19)
Intubation within 7 d, No. (%) No of events	n = 31 ; % = 31.3	n = 50 ; % = 50
Intubation within 14 d, No. (%) No of events	n = 34 ; % = 34.3	n = 51 ; % = 51
Ventilation-free days at day 28, median (IQR) Median (IQR)	28 (19 to 28)	24 (14 to 28)
Intensive care unit Median (IQR)	7 (5 to 13)	9 (5 to 18)
Hospital Median (IQR)	12 (9 to 20)	14 (9 to 23)
Mortality at day 14, No. (%) No of events	n = 6 ; % = 6.1	n = 6 ; % = 6
Mortality at day 28, No. (%) No of events	n = 8 ; % = 8.1	n = 16 ; % = 16
Cardiac arrest No of events	n = 2 ; % = 2	n = 6 ; % = 6
Supraventricular tachycardia or ventricular arrhythmia No of events	n = 3 ; % = 3	n = 1 ; % = 1
Atelectasis No of events	n = 1 ; % = 1	n = 0 ; % = 0
Suspected bacterial pneumonia	n = 13 ; % = 13.1	n = 17 ; % = 17

Outcome	High-flow oxygen therapy, , N = 99	Conventional oxygen therapy, , N = 100
No of events		
Bacteremia No of events	n = 7 ; % = 7.1	n = 11 ; % = 11

Perkins, 2022

Bibliographic Reference	Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, Bradley JM, Dark P, Dave C, De Soyza A, Dennis AV, Devrell A, Fairbairn S, Ghani H, Gorman EA, Green CA, Hart N, Hee SW, Kimbley Z, Madathil S, McGowan N, Messer B, Naisbitt J, Norman C, Parekh D, Parkin EM, Patel J, Regan SE, Ross C, Rostron AJ, Saim M, Simonds AK, Skilton E, Stallard N, Steiner M, Vancheeswaran R, Yeung J, McAuley DF; RECOVERY-RS Collaborators. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA. 2022 Jan 24. doi: 10.1001/jama.2022.0028. Epub ahead of print. PMID: 35072713.

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	ISRCTN16912075
Study start date	01-Apr-2020
Study end date	03-May-2021
Aim of the study	To identify the effectiveness and safety of continuous positive airway pressure (CPAP) and high-flow nasal oxygenation (HFNO) in adult hospitalised patients with acute respiratory failure due to COVID-19, deemed suitable for treatment escalation. Comparisons were made between each intervention and conventional oxygen therapy. The primary outcome was a composite of tracheal intubation or mortality within 30-days.
Country/geographical location	UK
Population description	1272 adult hospitalised patients with acute respiratory failure due to COVID-19, deemed suitable for treatment escalation participants across 48 UK hospitals.
Inclusion criteria	Adult (≥18-years) hospitalised patients with known or suspected COVID-19 were eligible if they had acute respiratory failure, defined as peripheral oxygen saturations (SpO2) of 94% or below despite receiving a fraction of inspired oxygen (FiO2) of at least

	0.4, and were deemed suitable for tracheal intubation if treatment escalation was required.
Exclusion criteria	We excluded patients with an immediate (<1-hour) need for invasive ventilation, known pregnancy, or planned withdrawal of treatment. A contraindication to an intervention, based on the judgement of the treating clinician, precluded randomisation to that trial arm.
Intervention dosage (loading)	CPAP or HFNO. In all participants, local policies, and clinical discretion informed decisions regarding choice of device, set-up and titration.
Intervention dosage (maintenance)	In all participants, local policies, and clinical discretion informed decisions regarding choice of device, set-up and titration.
Intervention scheduled duration	Participants randomised to CPAP or HFNO started treatment as soon as possible. Breaks from treatment were permitted for comfort. In all participants, local policies, and clinical discretion informed decisions regarding discontinuation of treatment.
Intervention actual duration	In all participants, local policies, and clinical discretion informed decisions regarding discontinuation of treatment.
Intervention route of administration	Local policies, and clinical discretion informed decisions regarding choice of device, set-up and titration. Tracheal intubation was performed when clinically indicated, based on the judgement of the treating clinician
Comparator (where applicable)	Conventional oxygen therapy via a face mask or nasal cannula.
Methods for population selection/allocation	Recruitment opened at 75 UK hospitals. Eligible participants were randomised using an internet-based system with allocation concealment. Randomisation was stratified by site, sex, and age, and the allocation was generated by a minimisation algorithm. A contraindication to an intervention, based on the judgement of the treating clinician, precluded randomisation to that trial arm. Randomisation: Study authors anticipated that either CPAP or HFNO might be unavailable at sites on a temporary or permanent basis. As such, the randomisation system allowed the treating clinician to randomise between CPAP, HFNO, and conventional oxygen therapy (on a 1:1:1 basis), or between a single intervention (CPAP/HFNO) and conventional oxygen therapy (on a 1:1 basis). Sites could not randomise between CPAP and HFNO only
Methods of data analysis	Intention-to-treat principle, including all randomly allocated participants.
Attrition/loss to follow-up	1277 randomisations across 48 UK hospitals. Five cases underwent double randomisation, leaving 1272 participants (380 CPAP; 417 HFNO; 475 conventional oxygen therapy). Eight participants withdrew and five patients were lost to follow-up.

	Primary outcome data were available for 99.0 % (1259/1272) of participants.
Source of funding	This study is funded by the National Institute for Health Research (NIHR) [COVID-19-RSC].
Study limitations (Author)	Planned sample size was not achieved with the decision to stop recruitment driven by practical reasons linked to reducing numbers of COVID-19 in the UK, and an ethical obligation to share accumulated data with the international clinical community. Secondly, there was crossover between allocated treatment arms, principally from the conventional oxygen therapy arm to one or both of the interventions. This is a common challenge in trials of non-invasive respiratory strategies, and reduces the observed effect size of a clinically effective treatment. Thirdly, it was impractical to collect screening data, meaning that the authors were unable to describe the number of non-randomised patients and reasons for non-randomisation. Finally, the trial was rapidly set-up early in the pandemic, prior to the development of a core outcome set for COVID-19 trials. Whilst the outcome list aligns closely to most of the core outcomes subsequently identified, the authors did not capture information on patient recovery following hospital discharge.
Study limitations (Reviewer)	Due to the nature of the trial interventions and context, the authors were unable to blind patients, treating clinicians, or outcome assessors.

Study arms
CPAP (N = 380)

HFNO (N = 417)

Conventional oxygen (N = 475)

Characteristics
Arm-level characteristics

Characteristic	CPAP (N = 380)	HFNO (N = 417)	Conventional oxygen (N = 475)
Age Mean (SD)	56.7 (12.5)	57.6 (13)	57.6 (12.7)
Male No of events	n = 260 ; % = 68.4	n = 272 ; % = 65.2	n = 312 ; % = 65.7
Female No of events	n = 120 ; % = 31.6	n = 145 ; % = 34.8	n = 163 ; % = 34.3
White No of events	n = 243 ; % = 64	n = 275 ; % = 66	n = 312 ; % = 65.7

Characteristic	CPAP (N = 380)	HFNO (N = 417)	Conventional oxygen (N = 475)
Black No of events	n = 16 ; % = 4.2	n = 14 ; % = 3.4	n = 19 ; % = 4
Asian No of events	n = 73 ; % = 19.2	n = 77 ; % = 18.5	n = 90 ; % = 19
Mixed No of events	n = 3 ; % = 0.8	n = 4 ; % = 1	n = 6 ; % = 1.3
Other No of events	n = 11 ; % = 2.9	n = 12 ; % = 2.9	n = 9 ; % = 1.9
Unknown No of events	n = 33 ; % = 8.7	n = 34 ; % = 8.2	n = 35 ; % = 7.4
None No of events	n = 148 ; % = 39	n = 140 ; % = 33.6	n = 188 ; % = 39.6
ESRF requiring RRT No of events	n = 2 ; % = 0.5	n = 6 ; % = 1.4	n = 5 ; % = 1.1
Congestive heart failure No of events	n = 2 ; % = 0.5	n = 4 ; % = 1	n = 5 ; % = 1.1
Chronic lung disease No of events	n = 65 ; % = 17.1	n = 52 ; % = 12.5	n = 66 ; % = 13.9
Coronary heart disease No of events	n = 34 ; % = 9	n = 26 ; % = 6.2	n = 44 ; % = 9.3
Dementia No of events	n = 4 ; % = 1.1	n = 1 ; % = 0.2	n = 3 ; % = 0.6
Diabetes requiring medication No of events	n = 86 ; % = 22.6	n = 98 ; % = 23.5	n = 91 ; % = 19.2
Hypertension No of events	n = 131 ; % = 34.5	n = 164 ; % = 39.3	n = 153 ; % = 32.2
Uncontrolled or active malignancy No of events	n = 7 ; % = 1.8	n = 10 ; % = 2.4	n = 7 ; % = 1.5

Characteristic	CPAP (N = 380)	HFNO (N = 417)	Conventional oxygen (N = 475)
Morbid obesity (BMI >35) No of events	n = 62 ; % = 16.3	n = 81 ; % = 19.4	n = 75 ; % = 15.8
COVID-19 status- no (%)			
Confirmed	409 (86.1)	326 (85.8)	355 (85.1)
Suspected	64 (13.5)	53 (14)	61 (14.6)
Clinical frailty Scale (pre-admission)_-no (%)			
CFS1- Very fit	62 (13.1)	72(19)	70 (16.8)
CFS2- well	237 (49.9)	192 (50.5)	196 (47)
CFS3- managing well	131 (27.6)	87 (22.9)	109 (26.1)
CFS4- vulnerable	30 (6.3)	12 (3.2)	27 (6.5)
CFS5- mildly frail	6 (1.3)	4 (1.1)	6 (1.4)
CFS6- moderately frail	3 (0.6)	3 (0.8)	0 (0)
CFS7- severely frail	0 (0)	0 (0)	2 (0.5)
CFS8- very severely frail	0 (0)	0 (0)	0 (0)
CFS9- terminally ill	0 (0)	0 (0)	0 (0)

Outcomes

Study timepoints

- 30 day

Outcome	CPAP vs Conventional oxygen, 30 day, N2 = 377, N1 = 356	HFNO vs Conventional oxygen, 30 day, N2 = 414, N1 = 368
Composite outcome: Tracheal intubation or mortality 30 days Adjusted Odds ratio/95% CI	0.67 (0.48 to 0.94)	0.95 (0.69 to 1.3)
Intubation within 30 days Adjusted Odds ratio/95% CI	0.66 (0.47 to 0.93)	0.96 (0.7 to 1.31)
Mortality at 30 days Adjusted Odds ratio/95% CI	0.91 (0.59 to 1.39)	0.96 (0.64 to 1.45)
Admission to critical care	0.69 (0.49 to 0.96)	1.06 (0.76 to 1.47)

Outcome	CPAP vs Conventional oxygen, 30 day, N2 = 377, N1 = 356	HFNO vs Conventional oxygen, 30 day, N2 = 414, N1 = 368
Adjusted Odds ratio/95% CI		
Median time to intubation Hazard ratio/95% CI adjusted	0.67 (0.52 to 0.86)	0.91 (0.72 to 1.14)
Mean length of stay in hospital Mean differences (95% CI), adjusted	-0.97 (-3.65 to 1.71)	0.7 (-1.93 to 3.34)
Mean length of stay in critical care **Mean difference (95% CI), adjusted**	-0.33 (-2.44, 1.78)	0.69 (-1.37, 2.75)

Composite outcome: Tracheal intubation or mortality - Polarity - Lower values are better
Intubation within 30 days - Polarity - Lower values are better
Mortality at 30 days - Polarity - Lower values are better
Admission to critical care - Polarity - Lower values are better

Outcome			
Serious adverse events (no) **By treatment arm**	CPAP	HFNO	Conventional oxygen
Pulmonary embolism	0	0	1
Type 2 myocardial infarction	1	0	0
surgical emphysema and pneumomediastinum	1	0	0
vomiting requiring emergency tracheal intubation	1	0	0
Intracranial bleed	1	0	0
Perforated bowel	1	0	0
Pneumothorax and pneumomediastinum	2	0	0

Risk of bias assessments

Grieco, 2021

Bibliographic Reference	Grieco, Domenico Luca; Menga, Luca S; Cesarano, Melania; Rosa, Tommaso; Spadaro, Savino; Bitondo, Maria Maddalena; Montomoli, Jonathan; Falo, Giulia; Tonetti, Tommaso; Cutuli, Salvatore L; Pintaudi, Gabriele; Tanzarella, Eloisa S; Piervincenzi, Edoardo; Bongiovanni, Filippo; Dell'Anna, Antonio M; Delle Cese, Luca; Berardi, Cecilia; Carelli, Simone; Bocci, Maria Grazia; Montini, Luca; Bello, Giuseppe; Natalini, Daniele; De Pascale, Gennaro; Velardo, Matteo; Volta, Carlo Alberto; Ranieri, V Marco; Conti, Giorgio; Maggiore, Salvatore Maurizio; Antonelli, Massimo; COVID-ICU Gemelli Study, Group; 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

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(This study was not blinded so bias could have been introduced when recording outcomes.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(This study was not blinded so bias could have been introduced when recording outcomes.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(This study was not blinded so bias could have been introduced when recording outcomes.)*
Overall bias and Directness	Overall Directness	Partially applicable.

		However, helmet NIV was applied continuously for at least 48 hours with high positive end-expiratory pressure and relatively low pressure support in centres with expertise with this technique. Not all centres would have this expertise.

Nair, 2021

Bibliographic Reference	Nair, Parvathy Ramachandran; Haritha, Damarla; Behera, Srikant; Kayina, Choro Athiphro; Maitra, Souvik; Anand, Rahul Kumar; Ray, Bikash Ranjan; Soneja, Manish; Subramaniam, Rajeshwari; Baidya, Dalim Kumar; Comparison of High-Flow Nasal Cannula and Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure Due to Severe COVID-19 Pneumonia.; Respiratory care; 2021

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (This study was not blinded so bias could have been introduced when recording outcomes.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (This study was not blinded so bias could have been introduced when recording outcomes.)
Overall bias and Directness	Overall Directness	Directly applicable

Ospina-Tascon Gustavo, 2021

Bibliographic Reference	Ospina-Tascon Gustavo, A; Calderon-Tapia Luis, Eduardo; Garcia Alberto, F; Zarama, Virginia; Gomez-Alvarez, Freddy; Alvarez-Saa, Tatiana; Pardo-Otalvaro, Stephania; Bautista-Rincon Diego, F; Vargas Monica, P; Aldana-Diaz Jose, L; Marulanda, Angela; Gutierrez, Alejandro; Varon, Janer; Gomez, Monica; Ochoa Maria, E; Escobar, Elena; Umana, Mauricio; Diez, Julio; Tobon Gabriel, J; Albornoz Ludwig, L; Celemin, Florez; Carlos, Augusto; Ruiz Guillermo, Ortiz; Caceres Eder, Leonardo; Reyes Luis, Felipe; Damiani Lucas, Petri; Cavalcanti Alexandre, B; HiFLo-Covid, Investigators; Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial.; JAMA; 2021; vol. 326 (no. 21); 2161-2171

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns (This study was not blinded so bias could have been introduced when recording outcomes. Also, measurements or estimations for the metabolic work of breathing, transpulmonary pressures, minute volume, or estimations of nonhomogeneous distribution of tidal ventilation were not performed; thus, potential mechanisms mediating the effect of high-flow oxygen therapy through a nasal cannula on the co–primary outcomes remain theoretical.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Overall bias and Directness	Risk of bias judgement	Some concerns (This study was not blinded so bias could have been introduced when recording outcomes.)
Overall bias and Directness	Overall Directness	Directly applicable

Perkins, 2022

Bibliographic Reference Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, Bradley JM, Dark P, Dave C, De Soyza A, Dennis AV, Devrell A, Fairbairn S, Ghani H, Gorman EA, Green CA, Hart N, Hee SW, Kimbley Z, Madathil S, McGowan N, Messer B, Naisbitt J, Norman C, Parekh D, Parkin EM, Patel J, Regan SE, Ross C, Rostron AJ, Saim M, Simonds AK, Skilton E, Stallard N, Steiner M, Vancheeswaran R, Yeung J, McAuley DF; RECOVERY-RS Collaborators. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA. 2022 Jan 24. doi: 10.1001/jama.2022.0028. Epub ahead of print. PMID: 35072713.

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

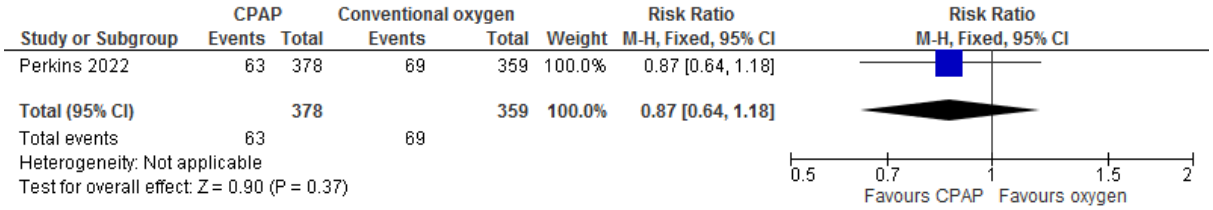
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns (This study was not blinded so bias could have been introduced when recording outcomes. There was 17.1% crossover between allocated treatment arms, principally from the conventional oxygen therapy arm to one or both of the interventions.)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (This study was not blinded so bias could have been introduced when recording outcomes. There was

		17.1% crossover between allocated treatment arms, principally from the conventional oxygen therapy arm to one or both of the interventions.)
Overall bias and Directness	Overall Directness	Directly applicable

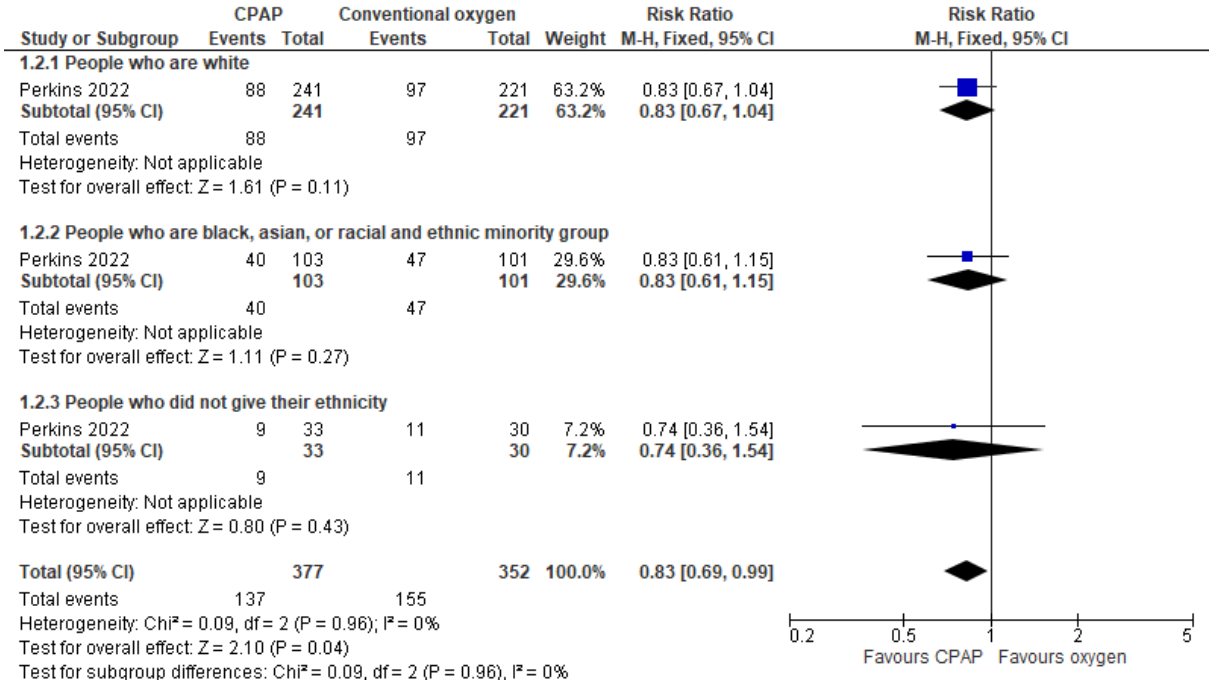
Appendix G: Forest Plots

CPAP versus conventional oxygen

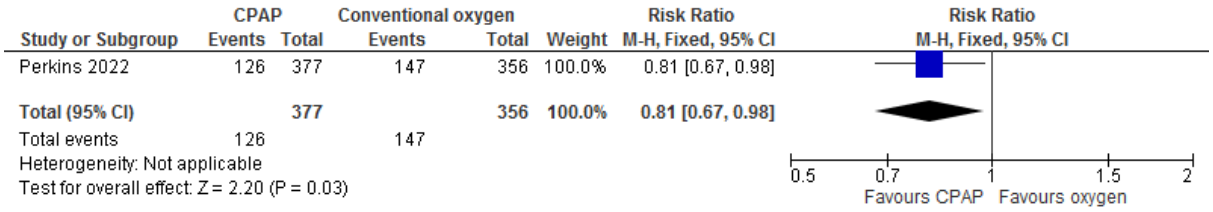
Mortality at 30 days



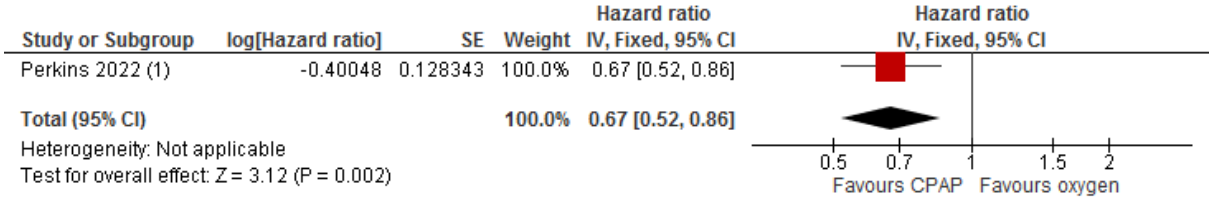
Composite outcome: Tracheal intubation or mortality at 30 days



Intubation within 30 days

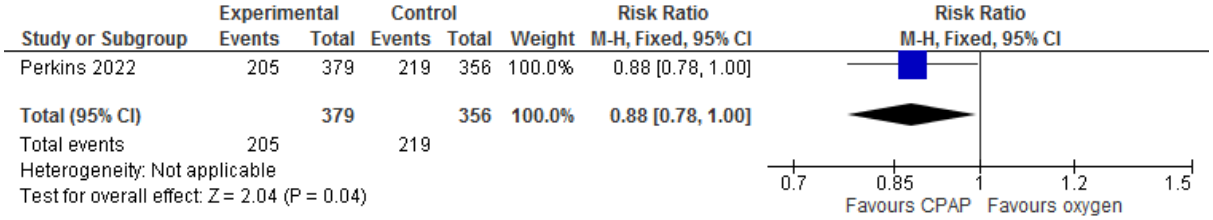


Median time to intubation

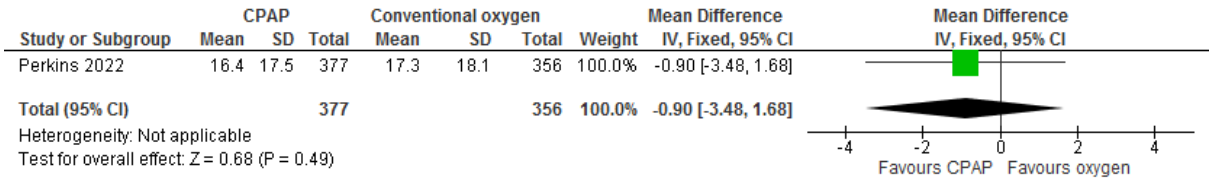


Footnotes
(1) Adjusted odds ratio

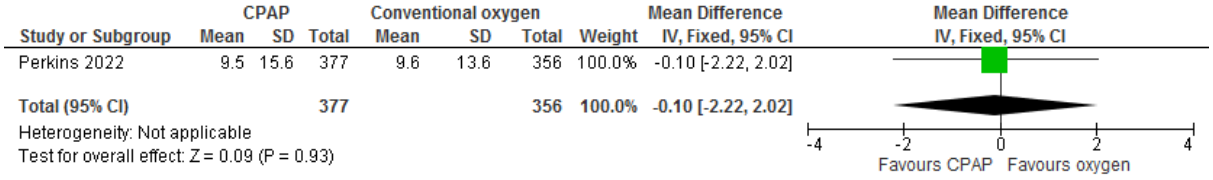
Admission to critical care



Mean length of stay in hospital (days)



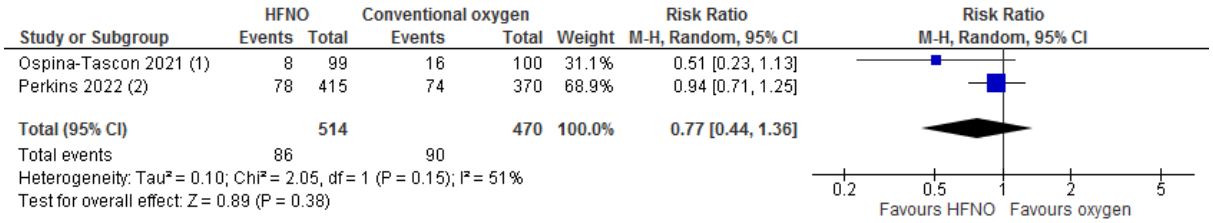
Mean length of stay in critical care (days)



HFNO versus conventional oxygen

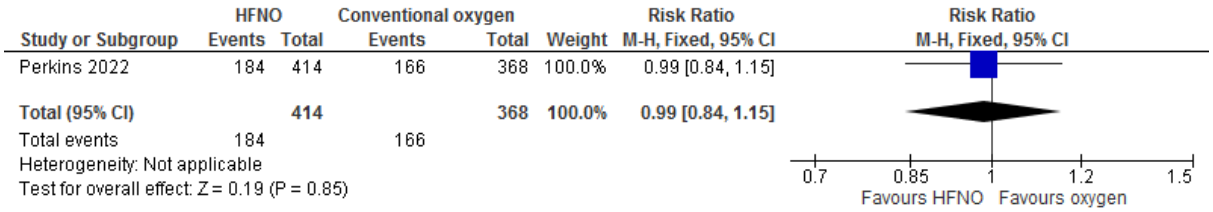
Mortality at 28 or 30 days

This data is presented using risk ratios to enable meta-analysis because hazard ratios are used in Ospina-Tascon 2021 and odds ratios are used in Perkins 2022.



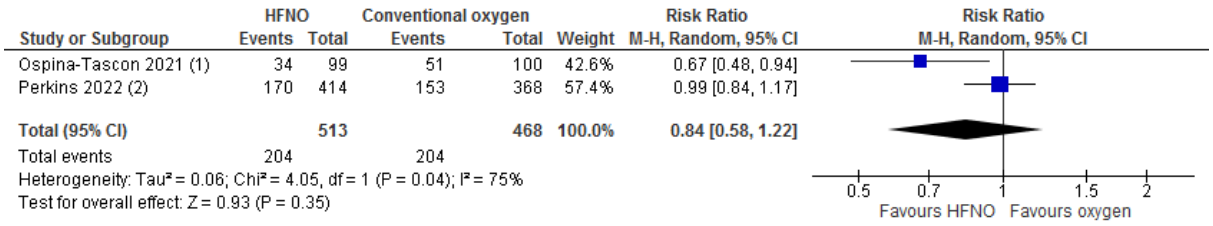
Footnotes
(1) Mortality at 28 days
(2) Mortality at 30 days

Composite outcome: Tracheal intubation or mortality at 30 days



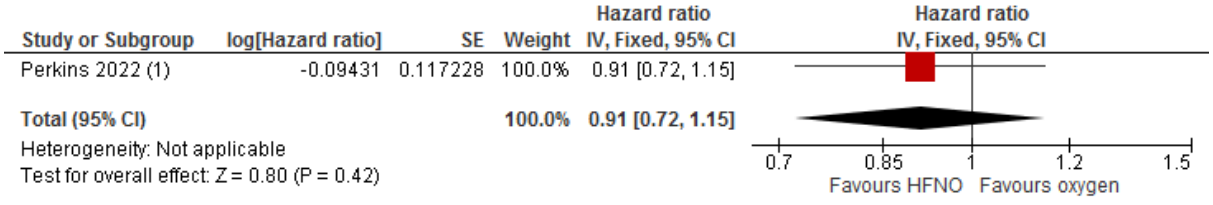
Intubation within 28 or 30 days

This data is presented using risk ratios to enable meta-analysis because hazard ratios are used in Ospina-Tascon 2021 and odds ratios are used in Perkins 2022.



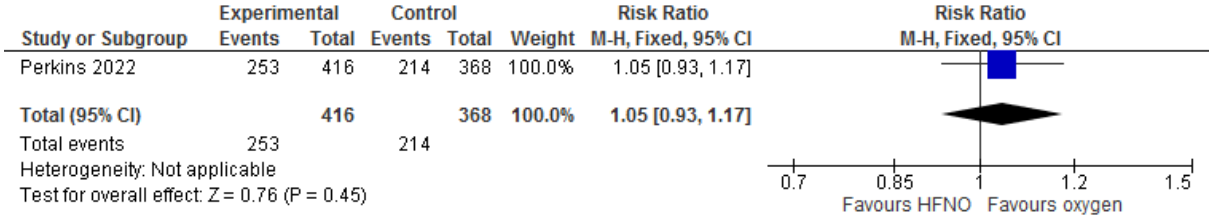
Footnotes
(1) Intubation within 28 days
(2) Intubation within 30 days

Median time to intubation

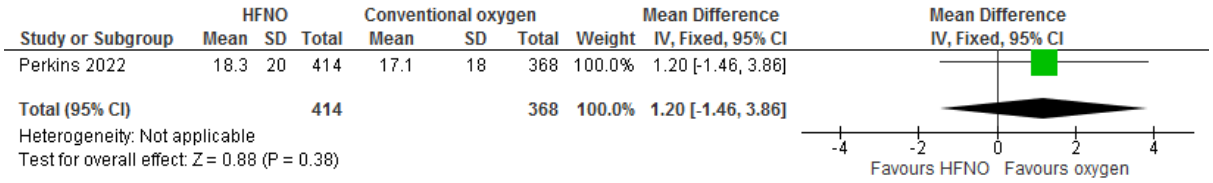


Footnotes
(1) Adjusted hazard ratio

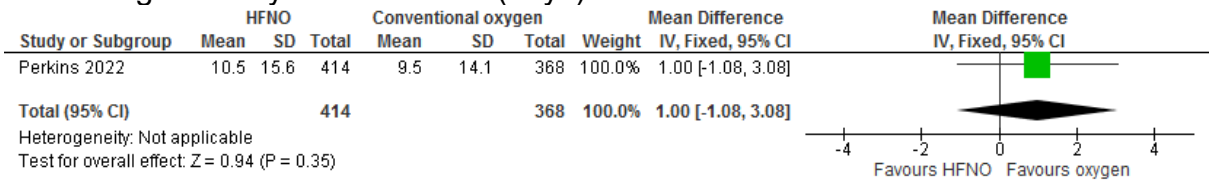
Admission to critical care



Mean length of stay in hospital (days)



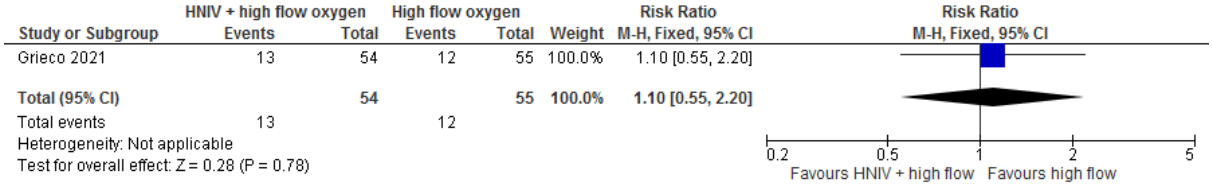
Mean length of stay in critical care (days)



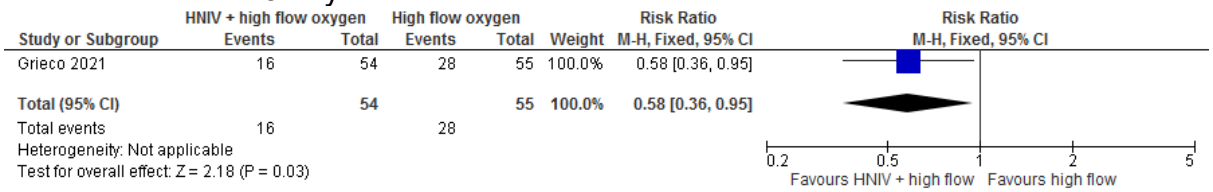
Helmet noninvasive ventilation followed by high-flow nasal oxygen versus high-flow oxygen alone

Mortality at 28 days

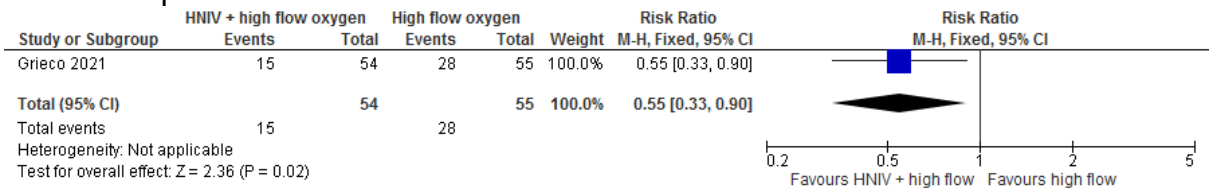
Mortality at 60 days



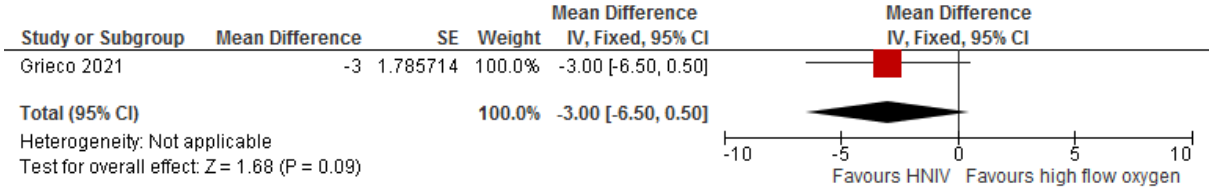
Intubation within 28 days from enrolment



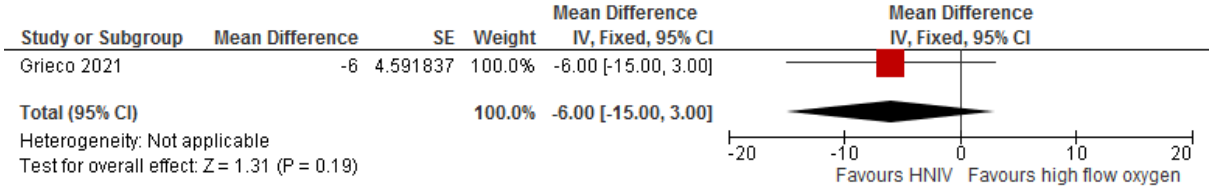
Intubation within 28 days from enrolment after adjudication of intubation criteria by external experts



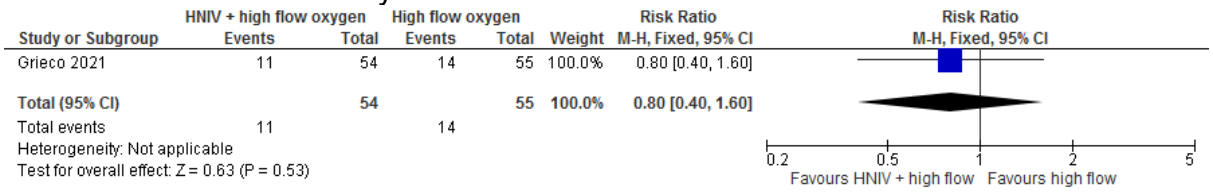
Invasive ventilation–free days at 28 days



Invasive ventilation–free days at 60 days

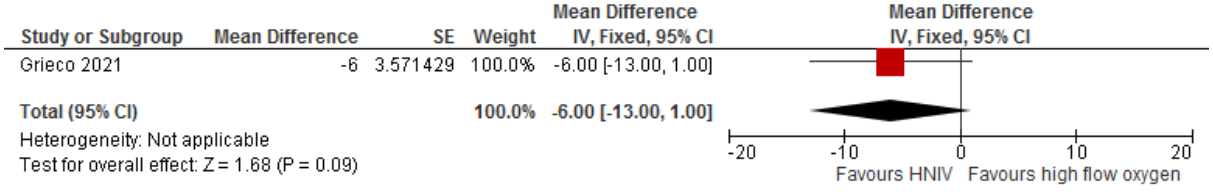


Intensive care unit mortality

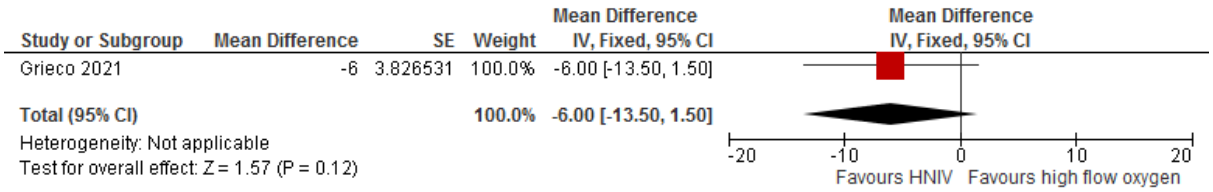


In-hospital mortality

Mean duration of stay: ICU (days)

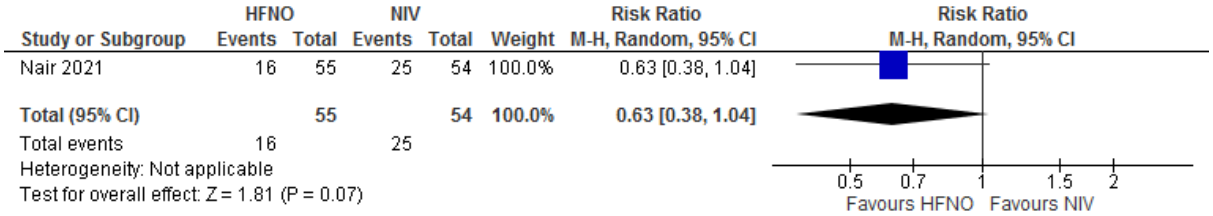


Mean duration of stay: hospital (days)

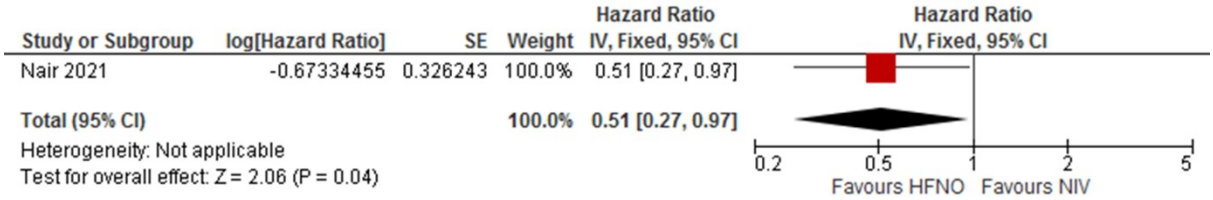


HFNO versus NIV

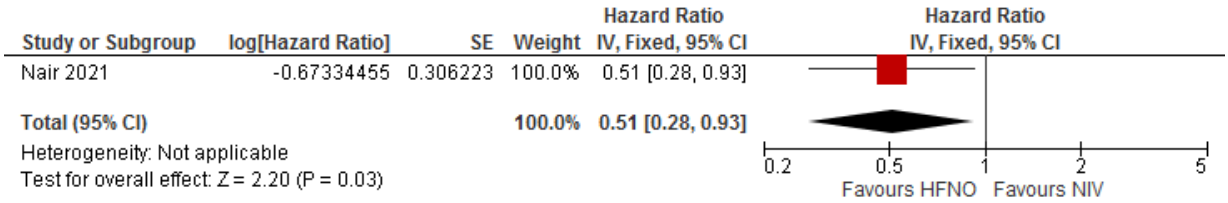
In-hospital mortality at 30 days



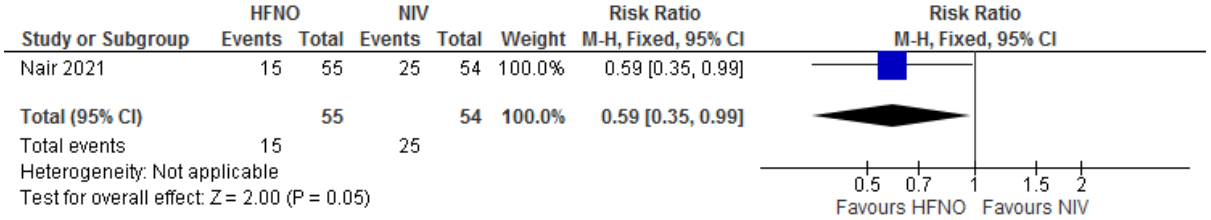
Intubation within 30 days



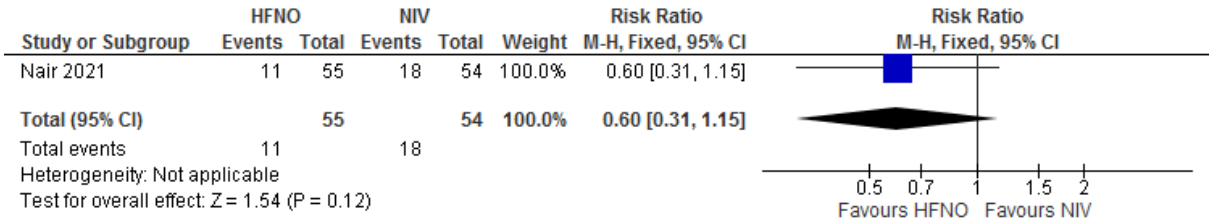
Tracheal intubation or mortality at 30 days



Intubation within 7 days



Intubation within 48 hours


HFNO
NIV
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Nair 2021 11 55 18 54 100.0% 0.60 [0.31, 1.15]
Total (95% CI) 55 54 100.0% 0.60 [0.31, 1.15]
Total events 11 18
Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)
0.5 0.7 1 1.5 2
Favours HFNO
Favours NIV

Appendix I: GRADE profiles

CPAP compared to conventional oxygen for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With conventional oxygen	With CPAP		Risk with conventional oxygen	Risk difference with CPAP
Mortality at 30 days											
737 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	Low	69/359 (19.2%)	63/378 (16.7%)	**RR 0.87** (0.64 to 1.18)	192 per 1,000	**25 fewer per 1,000** (from 69 fewer to 35 more)
Tracheal intubation or mortality at 30 days											
729 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	155/352 (44.0%)	137/377 (36.3%)	**RR 0.83** (0.69 to 0.99)	440 per 1,000	**75 fewer per 1,000** (from 137 fewer to 4 fewer)
Intubation within 30 days											
733 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	147/356 (41.3%)	126/377 (33.4%)	**RR 0.81** (0.67 to 0.98)	413 per 1,000	**78 fewer per 1,000** (from 136 fewer to 8 fewer)
Median time to intubation											
737 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	-	-	**HR 0.67** (0.52 to 0.86)	-	-

Certainty assessment							Summary of findings				
Admission to critical care											
735 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	219/356 (61.5%)	205/379 (54.1%)	**RR 0.88** (0.78 to 1.00)	615 per 1,000	**74 fewer per 1,000** (from 135 fewer to 0 fewer)
Mean length of stay in hospital											
733 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	Low	356	377	-	-	MD **0.9 lower** (3.48 lower to 1.68 higher)
Mean length of stay in critical care											
733 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	Low	356	377	-	-	MD **0.1 lower** (2.22 lower to 2.02 higher)

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, underpowered study
b. Confidence interval crosses line of no effect

HFNO compared to conventional oxygen for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With conventional oxygen	With HFNO		Risk with conventional oxygen	Risk difference with HFNO
Mortality at 28 or 30 days											
984 (2 RCTs)	serious[a]	not serious	not serious	serious[b]	none	Low	90/470 (19.1%)	86/514 (16.7%)	**RR 0.77** (0.44 to 1.36)	191 per 1,000	**44 fewer per 1,000** (from 107 fewer to 69 more)
Tracheal intubation or mortality at 30 days											
782 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	Low	166/368 (45.1%)	184/414 (44.4%)	**RR 0.99** (0.84 to 1.15)	451 per 1,000	**5 fewer per 1,000** (from 72 fewer to 68 more)
Intubation within 28 or 30 days											
981 (2 RCTs)	serious[a]	serious[c]	not serious	serious[b]	none	Very low	204/468 (43.6%)	204/513 (39.8%)	**RR 0.84** (0.58 to 1.22)	436 per 1,000	**70 fewer per 1,000** (from 183 fewer to 96 more)
Median time to intubation											
784 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	Low	-	-	**HR 0.91** (0.72 to 1.15)	-	-
Admission to critical care											

Certainty assessment							Summary of findings				
784 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	Low	214/368 (58.2%)	253/416 (60.8%)	**RR 1.05** (0.93 to 1.17)	582 per 1,000	**29 more per 1,000** (from 41 fewer to 99 more)
Mean length of stay in hospital (days)											
782 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	Low	368	414	-	-	MD **1.2 higher** (1.46 lower to 3.86 higher)
Median length of stay in hospital (days)											
199 (1 RCT)	serious[a]	not serious	not serious	very serious[d]	none	Very low	-	-	**OR 0.77** (0.47 to 1.26)	-	-
Mean length of stay in critical care (days)											
782 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	Low	368	414	-	-	MD **1 higher** (1.08 lower to 3.08 higher)
Median length of stay in critical care (days)											
199 (1 RCT)	serious[a]	not serious	not serious	very serious[d]	none	Very low	-	-	**OR 0.74** (0.45 to 1.22)	-	-

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.
b. Confidence interval crosses line of no effect
c. The magnitude of statistical heterogeneity was high, with I^2: 75%
d. Confidence interval crosses line of no effect, Low number of patients

Helmet NIV plus HFNO compared to HFNO for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With HFNO	With helmet NIV plus HFNO		Risk with HFNO	Risk difference with helmet NIV plus HFNO
Mortality at 28 days											
109 (1 RCT)	serious[a]	not serious	serious[b]	very serious[c]	none	Very low	10/55 (18.2%)	8/54 (14.8%)	**RR 0.81** (0.35 to 1.91)	182 per 1,000	**35 fewer per 1,000** (from 118 fewer to 165 more)
Mortality at 60 days											
109 (1 RCT)	serious[a]	not serious	serious[b]	very serious[c]	none	Very low	12/55 (21.8%)	13/54 (24.1%)	**RR 1.10** (0.55 to 2.20)	218 per 1,000	**22 more per 1,000** (from 98 fewer to 262 more)
In-hospital mortality											
109 (1 RCT)	serious[a]	not serious	serious[b]	very serious[c]	none	Very low	14/55 (25.5%)	13/54 (24.1%)	**RR 0.95** (0.49 to 1.82)	255 per 1,000	**13 fewer per 1,000** (from 130 fewer to 209 more)
Intensive care unit mortality											
109 (1 RCT)	serious[a]	not serious	serious[b]	very serious[c]	none	Very low	14/55 (25.5%)	11/54 (20.4%)	**RR 0.8** (0.4 to 1.6)	255 per 1,000	**51 fewer per 1,000** (from 153 fewer to 153 more)

Certainty assessment							Summary of findings				
Intubation within 28 days from enrolment											
109 (1 RCT)	serious[a]	not serious	serious[b]	not serious	none	Low	28/55 (50.9%)	16/54 (29.6%)	**RR 0.58** (0.36 to 0.95)	509 per 1,000	**214 fewer per 1,000** (from 326 fewer to 25 fewer)
Intubation within 28 days from enrolment after adjudication of intubation criteria by external experts											
109 (1 RCT)	serious[a]	not serious	serious[b]	not serious	none	Low	28/55 (50.9%)	15/54 (27.8%)	**RR 0.55** (0.33 to 0.90)	509 per 1,000	**229 fewer per 1,000** (from 341 fewer to 51 fewer)
Respiratory support free days											
109 (1 RCT)	serious[a]	not serious	serious[b]	very serious[c]	none	Very low	55	54	-	-	MD **2 days more** (2 fewer to 6 more)
Invasive ventilation free days (28 days)											
109 (1 RCT)	serious[a]	not serious	serious[b]	not serious	none	Low	55	54	-	-	MD **3 days more** (0 to 7 more)
Invasive ventilation free days (60 days)											
109 (1 RCT)	serious[a]	not serious	serious[b]	very serious[c]	none	Very low	55	54	-	-	MD **6 days more** (3 fewer to 15 more)
Duration of hospital stay (days)											
109 (1 RCT)	serious[a]	not serious	serious[b]	very serious[c]	none	Very low	55	54	-	-	MD **6 days fewer** (14 fewer to 1 more)

Certainty assessment							Summary of findings				
Duration of ICU stay (days)											
109 (1 RCT)	serious[a]	not serious	serious[b]	very serious[c]	none	Very low	55	54	-	-	MD **6 days fewer** (13 fewer to 1 more)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias
b. due to applicability of study design
c. Confidence interval crosses line of no effect, Wide confidence intervals, Low number of patients

HFNO compared to NIV for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With NIV	With HFNO		Risk with NIV	Risk difference with HFNO
In-hospital mortality at 30 days											
109 (1 RCT)	serious[a]	not serious	not serious	very serious[b]	none	Very low	25/54 (46.3%)	16/55 (29.1%)	**RR 0.63** (0.38 to 1.04)	463 per 1,000	**171 fewer per 1,000** (from 287 fewer to 19 more)
Intubation within 30 days											
109 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	-	-	**HR 0.51** (0.27 to 0.97)	-	-
Tracheal intubation or mortality at 30 days											
109 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	-	-	**HR 0.51** (0.28 to 0.93)	-	-
Intubation within 7 days											
109 (1 RCT)	serious[a]	not serious	not serious	not serious	none	Moderate	25/54 (46.3%)	15/55 (27.3%)	**RR 0.59** (0.35 to 0.99)	463 per 1,000	**190 fewer per 1,000** (from 301 fewer to 5 fewer)
Intubation within 48 hours											

Certainty assessment							Summary of findings				
109 (1 RCT)	serious[a]	not serious	not serious	very serious[b]	none	Very low	18/54 (33.3%)	11/55 (20.0%)	**RR 0.60** (0.31 to 1.15)	333 per 1,000	**133 fewer per 1,000** (from 230 fewer to 50 more)
Median (IQR) length of stay in hospital (days)											
serious[c]	none	not serious	not serious	serious[c]	none	Low	Hospital length of stay was 9 days (IQR 7, 13) for HFNO compared with 9 days (IQR 6, 12) for NI				

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

Explanations

a. The HFNC arm had awake prone positioning but the NIV arm did not adhere to awake prone positioning because of the practical difficulty with the NIV interface
b. Confidence interval crosses line of no effect, Low number of patients
c. The point estimates and interquartile ranges were similar.

Appendix I: Recommendations for research

Question	**Does a multidisciplinary team agreed approach to weaning from continuous positive airway pressure improve weaning times and result in stopping continuous positive airway pressure for people with COVID-19 and acute respiratory failure?**
Population	People with COVID-19 having continuous positive airway pressure for respiratory support I: multidisciplinary team agreed approach to weaning
Intervention(s)	Multidisciplinary team agreed approach to weaning
Comparator(s)	• standard care • different multidisciplinary team approaches
Outcomes	• patient experience • symptom improvement • length of time to wean • health-related quality of life

Question	**Is high-flow nasal oxygen effective in reducing breathlessness compared with standard care or conventional oxygen therapy for people in hospital with COVID-19 and respiratory failure when it is agreed that treatment will not be escalated beyond non-invasive respiratory support or palliative care is needed?**
Population	Adults over 18 years with COVID-19 having treatment for respiratory failure
Intervention(s)	High-flow nasal oxygen
Comparator(s)	• standard care • conventional oxygen therapy
Outcomes	• patient experience • symptom improvement • frequency of coughing • assessment of breathing pattern disorder • impact of breathlessness on activities of daily living such as eating, drinking and movement • recovery of sense of smell

	• practicalities of maintaining high-flow nasal oxygen at home for patients who wish their end of life care to occur at home