Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19 and acute respiratory failure patients, should high flow nasal oxygen therapy be used?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of high flow nasal oxygen therapy for patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy (low flow nasal cannula/face mask).	Low	Weak
We suggest the use of either high flow nasal oxygenation therapy or non-invasive positive pressure ventilation in patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy in the absence of any indication for emergent invasive mechanical ventilation.	Very low	Weak
We suggest the use of high flow nasal oxygen therapy for children with severe to critical COVID-19 who do not respond to conventional oxygen therapy (low flow nasal cannula/face mask).	Very low	Weak

Consensus Issues
The panel weakly suggests the use of high flow oxygen therapy after nil or suboptimal response to conventional oxygen therapy (low flow nasal cannula/face mask) which reflects the available evidence where most studies employed sequential oxygen supplementation. It should be noted however that a subset of patients may benefit from immediate intubation and contraindications to high flow nasal oxygen therapy such as facial deformities, uncooperative/combative patients, etc. should likewise be considered. The choice between high flow nasal oxygen therapy and non-invasive positive pressure ventilation will be influenced by the clinical indication (i.e., oxygenation vs. ventilation) and patient acceptability.

KEY FINDINGS

- Eight randomized controlled clinical trials were evaluated which investigated the efficacy of high-flow nasal oxygen therapy (HFNOT) among hospitalized COVID-19 patients with acute respiratory failure. HFNOT was compared to conventional oxygen therapy (COT) (face mask, venturi face mask, non-rebreather face mask) and non-invasive ventilation (NIV) (CPAP, Helmet).

- For HFNOT vs COT, pooled results showed benefit with regards to improvement of PaO_2/FiO_2 ratio and changes in respiratory rate among patients who received HFNOT compared to those receiving COT. In addition, a trend towards benefit can be seen in terms of 28-day mortality, need for

intubation, length of hospital stay, and length of ICU stay to those in the HFNOT group compared to those in the COT. With regards to changes in heart rate, clinical recovery, and ventilator-free days, no significant difference was found between the two groups. The certainty of evidence is low due to serious risk of bias and imprecision.

- For the comparison between HFNOT and NIV, a trend towards benefit can be observed in patients in the HFNOT group in terms of 28-day mortality. However, with regards to the need for mechanical ventilation, results shows that there is less need for mechanical ventilation in those who were in the NIV treatment group. No significant difference is observed in hospital length of stay and ventilator free days between the two groups. The certainty of evidence is very low due to serious risk of bias, inconsistency, and imprecision.

WHAT'S NEW IN THIS VERSION?

Four new randomized controlled trials were added for this review to evaluate the use of high-flow nasal oxygen therapy (HFNOT) therapy in COVID-19 patients. The previous recommendation was extrapolated from 3 published randomized controlled trials (RCT) and one pre-print RCT. Also, in this review, the studies comparing HFNC to Conventional Oxygen Therapy (COT) and Non-invasive ventilation (NIV) were appraised and examined together.

PREVIOUS RECOMMENDATIONS
As of 01 December 2021

We suggest the use of high flow nasal cannula for patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy (low flow nasal cannula/face mask). *(Low certainty of evidence; Weak recommendation)*

Consensus Issues
For HFNC vs COT
The use of high flow nasal cannula should only be considered when patients fail to respond to low flow nasal cannula or face mask. It is not intended to be the immediate first line respiratory support for COVID-19 patients. It was initially promoted due to its capability to deliver high oxygen concentration, particularly when coupled with the potential harm or risk of viral aerosolization with non-invasive ventilation. The comparison of the efficacy of high flow nasal cannula and non-invasive ventilation is discussed in a separate review.

We suggest the use of either high flow nasal cannula or non-invasive positive pressure ventilation in COVID-19 patients with hypoxemic respiratory failure in the absence of any indication for emergent invasive mechanical ventilation. *(Low certainty of evidence; Weak recommendation)*

Consensus Issues
For HFNC vs NIV
The risk of aerosolization using non-invasive ventilation was not discussed in the identified studies, but case series and reports have suggested minimal risk for health care workers. Standard operating procedure includes the use of filters in the expiratory limb tubing for non-invasive ventilation and use of face masks for patients on high flow nasal cannula. Physicians must be cognizant of the indications for intubation such as continued and progressive deterioration, and signs of respiratory failure.

INTRODUCTION

As of 2022, the SARS-Cov-2 pandemic has caused more than 6 million mortalities around the world because of the unfavorable outcomes related to acute hypoxemic respiratory failure [1-3]. Locally, registered deaths due to COVID-19 have been cited as the 8th most common cause of for a total of 11,677 deaths or 4.4% of the total deaths from January to June 2022 [4]. Local descriptive studies done reported that upon admission, significant proportion of non-survivors presented with acute respiratory failure and necessitated oxygen support or mechanical ventilation [5]. Though the best option for non-invasive respiratory support systems in the management of acute hypoxemic respiratory failure is still a matter of discussion, high flow nasal oxygen therapy (HFNOT) emerged as an effective and well-tolerated respiratory support technique in different clinical scenarios [2,6].

REVIEW METHODS

We performed a comprehensive and systematic literature search to identify relevant studies in PubMed, Cochrane Library, WHO trial Registry, ClinicalTrial.gov and Covid-19 NMA databases up to October 30, 2022. A preprint search was also done in medRxiv and bioRxiv. Our search strategy combined concepts related to High Flow Nasal Cannula, Covid-19, Acute Respiratory Failure, and Randomized Controlled Trial. MeSH and free text search were done. The search combination used were as follows: ('HFNC' OR 'high-flow nasal cannula' OR 'high-flow nasal oxygen' OR 'high-flow oxygen') AND ('COVID 19' OR 'SARS CoV 2' OR 'Severe Acute Respiratory Syndrome Coronavirus 2 Infection' OR 'COVID-19') AND/OR ('ARDS' OR 'Acute Respiratory Distress Syndrome' OR 'Acute Respiratory Failure' OR 'Respiratory Failure') AND/OR ('Ventilation, Noninvasive' OR 'Non Invasive Ventilation' OR 'Noninvasive Ventilation') AND/OR ('Conventional Oxygen Therapy' OR 'Oxygen therapy') AND ('Randomized Controlled Trial' OR 'Controlled Trial') OR ('Meta-analysis' OR Metaanalysis). We also reviewed the references listed in each identified study and manually searched the related articles to identify all eligible studies and minimize any potential publication bias. No language or journal type restriction was applied. (See Appendix 2: PRISMA)

RESULTS

Four new RCTs were added to the existing data from the Adult LCPG Phase II, all of which were evaluated to have unclear to high-risk of selection and detection biases as well as imprecision and inconsistency in most of the critical outcomes.

Characteristics of study population, interventions, and comparators

Three of the included studies were single-center RCTs [7-9] and the rest were multicenter studies [10-14]. All of the trials reviewed were published and can be seen in the COVID-19 NMA initiative except for the study by Frat 2022 [14]. A total of 2,905 patients were included in this meta-analysis. Patients were randomized to HFNOT (n=1,237), NIV (n=488), and COT (1,180) across all studies. Five studies compared high flow nasal oxygen therapy (HFNOT) to conventional oxygen therapy (using simple oxygen facemask, non-rebreather face mask, and venturi facemask among others) and 2 studies compared HFNOT to non-invasive ventilation primarily utilizing CPAP and Helmet CPAP. One study [13], was a parallel, 3-group, randomized clinical trial designed to evaluate the clinical effectiveness of CPAP or HFNOT, compared with conventional oxygen therapy, in hospitalized patients with acute hypoxemic respiratory failure due to COVID-19.

Study participants in seven of the eight trials were aged 18 and above while 1 study included patients 16 years of age and above [8]. Inclusion criteria were suspected or laboratory confirmed SARS-CoV-2 infection, presence of pulmonary infiltrates, and clinical signs of acute respiratory infection. Two trials only included patients who met the diagnostic criteria for severe COVID-19 [7,9]; one study only included patients with mild hypoxemia fulfilling an arterial partial pressure of oxygen to fraction of inspired oxygen ratio of <300 in room air [10]; while the remaining studies included patient under the moderate to severe category [8,11-14]. Patients were excluded if the following criteria were met: 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 edema, presence of acute or chronic heart failure, clinical suspicion or confirmation of peripheral demyelinating disease, history of advanced chronic

obstructive pulmonary disease, advanced liver cirrhosis, 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.

Three trials reported on adverse events [10,11,14] and two studies reported on escalation of respiratory support [8,10]. Only one study reported on the ROX index between patients allocated to the HFNOT group vs the COT group [12].

All patients received treatments in accordance with the clinical judgement of treating physicians, local protocols and routine clinical practice. The allocated treatments were started as soon as possible, usually within 30 minutes from randomization. Patients randomized to conventional oxygen therapy (COT) received oxygen via standard facemask, low-flow nasal cannula, non-rebreather facemask [8,14], or Venturi facemask [10]. The patients in the HFNOT group received heated humidified HFNO, the initial flow rate of which was set at 40L/min and increased as required up to 60L/min, according to patient tolerance. The temperature was set from 37°C to 31°C according to patient comfort. A surgical mask was typically placed over the HFNO cannula. Lastly, the patients in the non-invasive ventilation utilized either CPAP [13] or helmet device [7,11]. Criteria for considering either escalation of respiratory support, intubation or weaning off study interventions were defined, observed, and followed. (Appendix 3: Characteristics of included studies).

Overall certainty of evidence

The overall certainty of evidence was rated low between HFNOT vs COT and very low between HFNOT vs NIV due to the presence of serious risk of bias, inconsistency, and imprecision. All included studies are open-label trials and lacked the possibility of blinding, which may affect the assessment of outcomes. In addition, the sample size of some of the included trials [7-9,11] were relatively small and therefore, small variations in the number of events may have rendered treatment effect on the primary outcomes non-significant. Other than this, one study did not achieve its planned sample size due to the decision to stop recruitment early which may have underpowered the analysis to detect small but clinically important treatment effects [13]. Also, even if the clinical criteria used to decide on the cessation or escalation of respiratory support were standardized, the subjectivity in clinical judgement could not be excluded.

Efficacy outcomes

Mortality outcomes

Based on the pooled results of five out of the eight studies comparing HFNOT and COT, there was a trend towards benefit in mortality at day 28 between those who were randomized to HFNC versus COT, though not statistically significant, (RR 0.89; 95% CI 0.72-1.1; I^2=0%; moderate certainty). This is also the case between HFNOT vs NIV wherein pooled results from 3 studies showed (RR 0.94: 95% CI 0.6-1.48; I^2=52%; very low certainty). There was substantial level of heterogeneity at I^2=52%. In HFNOT vs NIV heterogeneity can be attributed to differences in some co-interventions involved [13], and minor clinical differences in inclusion criteria.

With regards to the need for mechanical ventilation, pooled results showed a trend towards benefit, though not statistically significant, between HFNOT vs COT (RR 0.83, 95% CI 0.67-1.02; I^2=62%; low certainty). While between the HFNOT vs NIV, pooled results shows that there is less need for mechanical ventilation in patients who received NIV (RR 1.21, 95% CI 1.00-1.46; I^2=81%; very low certainty). Significant heterogeneity for both groups can be due to lack of standardized criteria in some studies on when to intubate while in the studies which set a standardized criterion, the subjectivity in clinical judgement cannot be excluded.

There was also a trend towards benefit in the length of ICU stay (MD -0.7 days, 95% CI -1.4 to 0.0; I^2=0%; low certainty) and hospital stay (MD -0.72 days, 95% CI -2.65 to 1.2; I^2=13%; low certainty) between the HFNOT and COT groups. On the other hand, no data can be pooled with regards to ICU stay in the HFNOT and NIV groups, but the study by Grieco et al. [11] showed similar trend in results wherein the median numbers of days in the ICU were 9 days (IQR, 4-17 days) in the helmet group vs 10 days (IQR, 5-23 days)

in the high-flow nasal oxygen group (Absolute Risk Difference -6 days; 95% CI -13 to 1). Pooled data on hospital stay showed no observed difference between HFNOT and NIV (MD -0.58 days, 95% CI -36.27 to 37.42; I^2=0; low certainty).

For Ventilator Free Days, there is no significant difference in both HFNC vs COT and HFNC vs NIV groups with (MD 3.91 days, 95% CI -17.46 to 25.27; I^2=0%; low certainty) and (MD -0.94 days, 95% CI -27.04 to 25.16; I^2=0%; low certainty) respectively.

Other important outcomes

Changes in heart rate, respiratory rate, and PaO_2/FiO_2 ratio

Changes in HR, RR, and PaO_2/FiO_2 were presented in three studies [8,9,12] for HFNC vs COT. After treatment, RR was lower in the HFNOT group than in the COT group (MD -1.67, 95% CI -2.92 to -0.41; I^2=86%; very low certainty) and PaO_2/FiO_2 was higher in the HFNC oxygen therapy group than in the COT group (MD 34.6, 95% CI 32.4-36.8; I^2=0%; low certainty). Similar results are shown in the study Perkins et al. [13] which showed lower respiratory rate with concomitant higher PaO_2/FiO_2 ratio in patients on HFNOT compared to those in COT. With regards to changes in heart rate, no significant difference was observed between the two groups (MD -1.52, 95% CI -1.91 to 4.95; I^2=78%; very low certainty).

No pooled results can be done between HFNC vs NIV, however, results from studies by Nair et al. and Grieco et al. [7,11] showed that no difference in respiratory rate between the two groups but higher PaO_2/FiO_2 can be observed in the NIV group (using Helmet CPAP) with the results from Grieco et. al showing a mean (SD) PaO_2/FiO_2 in the helmet group of 188 (73) vs 138 (46) in the high-flow nasal oxygen group (MD 59; 95% CI, 39-61; P < .001) [11]. No significant differences in heart rate were observed between HFNOT vs COT (MD -0.6, 95% CI -0.84 to -2.04; low certainty).

ROX index

One study measured ROX index as an outcome between patients who received HFNOT and COT. ROX index is a validated measurement that predicts the need to intubate in patients who received high flow nasal oxygen therapy to treat hypoxemic respiratory failure [15]. A ROX score of ≥4.88 predicts lower risk of progressing to mechanical ventilation. The use of HFNOT when compared to COT showed significantly higher ROX index at two (MD 2.06; 95% CI 1.61-2.51; low certainty) and four (MD 2.07; 95% CI 1.60-2.54) hours post-randomization. No data comparing ROX index between patients who received HFNC and NIV was available.

Interventions	ROX Index at 2 hours Mean±SD	ROX Index at 4 hours Mean±SD
HFNC (n=109)	6.3881±1.9834	6.8296±4.7596
COT (n=111)	4.3302±1.3595	4.7596±1.4421

Safety outcomes

Adverse events and serious adverse events

Two studies reported on adverse events. One comparing HFNOT vs COT [14] and the other one between HFNOT vs NIV (Helmet CPAP) [11]. The most common adverse events in all groups were ventilator-associated pneumonia (VAP), followed by septic shock then by pneumothorax. In the HFNOT vs COT group, there is no significant difference in the risk of developing VAP and septic shock between the two groups (RR 1.09, 95% CI 0.9-1.32) and (RR 0.99, 95% CI 0.63-1.55) respectively. In terms of pneumothorax, subjects in the HFNC group have a higher risk of this adverse event (RR 1.45, 95% CI 0.39-5.31). For HFNC vs NIV group, there is a trend towards higher risk of having VAP (RR 1.26, 95% CI 0.7-2.27), septic shock (RR 1.69, 95% CI 0.89-3.2), and pneumothorax (RR 1.96, 95% CI 0.37-10.26) in patients randomized in the HFNOT group.

High flow nasal oxygen therapy in children

Based on literature, children are less commonly affected by COVID-19, the severity of disease is less, and mortality is <1% [33]. Thus, the data on respiratory support and mechanical ventilation is scarce in the pediatric population. At present, there are no randomized clinical trials assessing the effect of different ventilatory support in the pediatric population who presents with life-threatening complications like ARDS, severe pneumonia, or septic shock in context of COVID-19. Most of the data are indirect and are extrapolated from literature and guidelines on adults with COVID-19 and evidence from other viral respiratory infections.

A case report by Van Gorp [34] described a 15-year-old boy with severe COVID-19 who was successfully managed with HFNOT. The case showed clinical improvement with reduced work of breathing during the first hours after starting HFNOT [34]. The authors have then concluded that HFNO can be safely used as respiratory support therapy in pediatric patients with COVID-19 with the use of aerosol mitigating interventions considered. Thus, in children, HFNO or NIV are safe and efficacious modes of respiratory support which may provide adequate respiratory support to prevent the need for invasive mechanical ventilation for those with mild ARDS without hemodynamic instability, with strict close monitoring [35].

RECOMMENDATIONS FROM OTHER GROUPS

Five guidelines on the non-invasive ventilatory management of COVID-19 were identified. These are the same recommendations stated on the previous update. No new guidelines are released by the following medical society/groups as of 05 November 2022.

Group / Society / Network	Year	Recommendation	Level of Evidence / Strength of Recommendation
The Australian and New Zealand Intensive Care Society (ANZICS) [22]	2020	High flow nasal oxygen (HFNO) therapy (in ICU): HFNO is a recommended therapy for hypoxia associated with COVID-19 disease, as long as staff are wearing optimal airborne PPE	None stated
European Respiratory Journal [23]	2021	We suggest HFNC or non-invasive CPC delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxemic acute respiratory failure without an immediate indication for invasive mechanical ventilation	Conditional recommendation Very low certainty of evidence
National Institutes of Health [24]	2020	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV)	BIIa
World Health Organization [25]	2021	In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) may be used	Conditional recommendation
Society of Critical Care Medicine [26] Surviving Sepsis Campaign	2021	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, we suggest using HFNC over conventional oxygen therapy	Weak recommendation
		In adults with COVID-19 and acute hypoxemic respiratory failure, we suggest using HFNC over NIPPV	Weak recommendation
COVID-19 PICU Guidelines: For High- and Limited-Resource Settings [35]	2020	Children with COVID-19 that remain with increased work of breathing and hypoxemia should be escalated to high flow nasal cannula (HFNC) if available. Patients with progressive respiratory distress or where HFNC is unavailable can be escalated to noninvasive positive pressure ventilation (NIPPV), bubble continuous positive	Strong recommendation

		airway pressure (bCPAP) or bilevel positive airway pressure (BiPAP)	

ONGOING STUDIES AND RESEARCH GAPS

As of 05 November 2022, there are 8 ongoing trials comparing the use of High flow nasal oxygen therapy to either that of Conventional Oxygen Therapy and Non-invasive ventilation. (Appendix 7: Characteristics of ongoing trials)

More high-quality clinical trials determining the effectiveness of HFNOT in improving critical and clinically important outcomes are needed. Also, future studies should take into consideration the different surges of the pandemic, including the presence of different SARS-CoV-2 variants, and the differences in vaccination status of the participants, which may have various indirect consequences on the results being analyzed.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST, PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

HFNOT has been proposed as an alternative to conventional oxygen therapy (COT) or non-invasive ventilation (NIV) in some subgroup of patients with acute hypoxemic respiratory failure [16]. Other than this, HFNOT could be a valuable and practicable treatment option for patients with COVID-19 pneumonia, with remarkable clinical advantages compared to other interventions. It is easy to set-up and can be taught even for non-expert personnel with varied backgrounds [17]. Locally, it is more accessible and available [18,19]. Hence, its application in a non-ICU setting might be crucial for countries and health-care systems with shrinking critical care and invasive ventilation resources [20,21].

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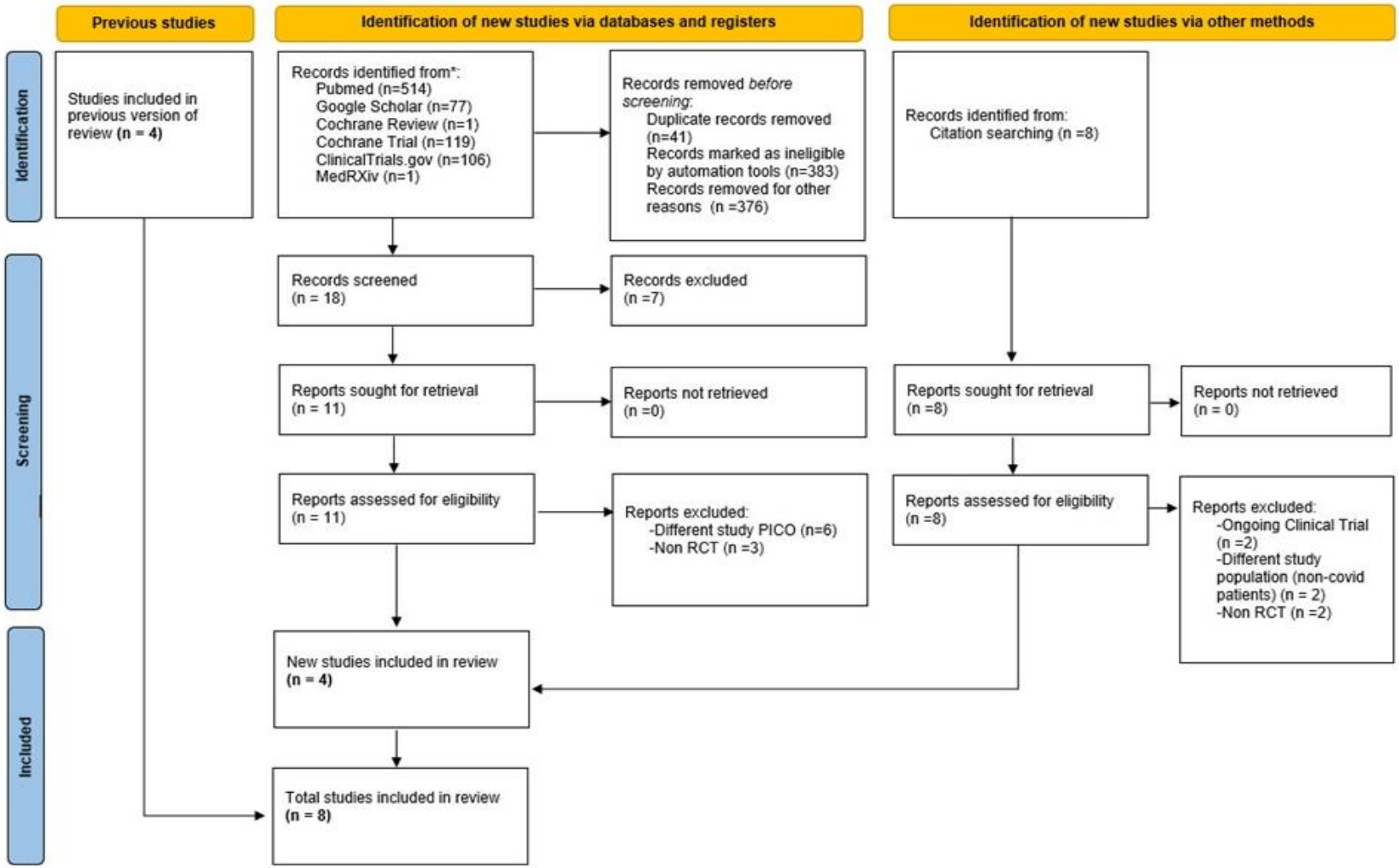
Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7/10)

FACTORS	JUDGEMENT				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)			
Benefits	Large (2)	Moderate (5)	Small	Varies	**RR was lower in the HFNO group** than in the COT group (MD -1.57, 95% CI -2.03 to -1.11; Low Certainty) **PaO_2/FiO_2 was higher in the HFN oxygen therapy group** than in the COT group (MD 34.6, 95% CI 32.4-36.8; Moderate Certainty). Similar results are shown in the studies done by Ospina-Tascon et al.[12] and Perkins et al.[13] which showed **lower respiratory rate with concomitant higher PaO_2/FiO_2 ratio in patients on HFNO compared to those in COT.** **Results were inconclusive for HFNOT vs NIV, with only trend towards benefit for mortality.**
Harm	Large	Moderate (1)	Small (4)	Uncertain (2)	No significant difference in the risk of having VAP and septic shock between the two groups (RR 1.09, 95% CI 0.9-1.32; P=0.3593) and (RR 0.99, 95% CI 0.63-1.55; P=0.9704) respectively. In terms of **pneumothorax**, subjects in the **HFNC group have a higher propensity** of this adverse event (RR 1.45, 95% CI 0.39-5.31; P=0.5725). On the other hand, between the HFNC vs NIV group there is a **trend towards higher risk of having VAP, septic shock, and pneumothorax in patients randomized in the HFNC group** (RR 1.26, 95% CI 0.7-2.27; P=0.437); (RR 1.69, 95% CI 0.89-3.2; P=0.1052); and (RR 1.96, 95% CI 0.37-10.26; P=0.4243) respectively.
Certainty of Evidence	High	Moderate	Low (7)	Very low	Low

Balance of effects	Favors intervention (1)	Probably favors intervention (6)	Does not favor intervention	Probably favors no intervention	Favors no intervention	Varies	HFNC is still suggested to be an effective and safe treatment modality in acute respiratory failure with optimal settings and selection of ideal patient.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain / Varies	Large cost (4)	Moderate cost (3)	Negligible cost	Moderate savings	Large savings	A report from DOH has shown that 1 unit of HFNC costs ₱118,500. The daily rate of HFNC machine use ranges from ₱1,100.00 to ₱2,030.00. On the other hand, the daily rental of machines used for other non-invasive ventilatory support amounts from ₱1,840.00 to ₱2,860.00.[32]
Certainty of evidence of required resources	No included studies (1)	Very low	Low	Moderate (3)	High (2)		Costs for HFNC differ depending on the severity of a patient and the duration of treatment.
Cost effectiveness	No included studies (1)	Probably / Favors the comparison (2)	Probably favors the intervention (4)	Favors the intervention (1)	Varies		Direct comparison of costs of HFNC versus other non-invasive modalities is not possible due to limited data and due to varied cost per hospital.
Equity	Varies (1)	Reduced (1)	Probably reduced (2)	Probably no impact	Probably increased (4)	Increased	
Acceptability	Varies	No Probably no	Yes (2)	Probably yes (5)			For the use: 7 Against the use: 0
Feasibility	Varies	No Probably no	Yes (2)	Probably yes (5)			

Appendix 2: Search Yield and Results – PRISMA Flow Diagram



Appendix 3: Characteristics of Included Studies (n=8)

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/Control	Outcomes
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 Ospina-Tascon et. al (2021) December 2021 IDENTIFIER: 10.1001/jama.2021.20714 **MODERATE TO SEVERE**	Randomized, open-label clinical trial	Colombia	220	**Inclusion Criteria:** -Age 18 years or older; - Suspected or confirmed infection by SARS-CoV-2; -Acute respiratory distress with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2) < 200; - Clinical signs of respiratory failure: laborious breathing, use of accessory muscles and respiratory rate greater than 25/min; -Less than 6 hours from fulfilling the criteria of acute respiratory failure **Exclusion criteria:** -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 edema -history of or current left ventricular ejection fraction of less than 45% -history of chronic heart failure -clinical suspicion or confirmation of peripheral demyelinating disease -history of advanced chronic obstructive pulmonary disease	In the high-flow oxygen therapy group, respiratory support was continuously applied through large-bore binasal prongs using heated and humidified gas at an initial flow of 60 L/min and an Fio2 of 1.0. 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. 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 Spo2 values of 92% or greater with less than 9 L/min of conventional oxygen therapy.	In the conventional oxygen therapy group, oxygen was applied continuously through any low-flow oxygen device or combination thereof (nasal prongs, mask with or without oxygen reservoir, Venturi mask systems). Rates of gas flow and Fio2 were adjusted to maintain Spo2 values of 92% or greater until patient intubation or recovery.	**Primary Outcomes** -Need for intubation within 28 days after randomization -Time to clinical recovery within 28 days after randomization **Secondary Outcomes** -Proportion of patients requiring early intubation -Mechanical ventilation at days 7 and 14 -Mechanical ventilation free-days within 28 days -Renal replacement therapy-free days -Hospital and intensive care unit length of stay -Overall mortality by day 28 -Proportion of adverse events **Tertiary Outcomes** -time-course of oxygen flow and PaO2/FiO2 ratio -Time (in hours) from randomization up to intubation -Clinical evolvement of multiorgan dysfunction evaluated by (SOFA) score (1), calculated day-by-day from randomization up to day-7 and then, at day-10 and 14 (if hospitalized at such time points) -Evolvement of extra-pulmonary organ dysfunction evaluated by the extra pulmonary score given by the Sequential Organ Failure Assessment Score (SOFA) score -Relationship between HACOR and ROX scales and requirement of intubation -Time-course of some prespecified blood markers: IL-6, IL-8, leucocytes, neutrophil: lymphocyte ratio, platelet count, lactate dehydrogenase, ferritin, D-Dimer.

				-hospitalization due to chronic obstructive pulmonary disease decompensation within the last year -advanced liver cirrhosis -anatomical or other conditions precluding the use of a high-flow nasal cannula -do-not-intubate or do-not-resuscitate orders -imminent death -refusal of study participation by a patient or their next of kin.			
The effectiveness of high-flow nasal cannula and standard non-rebreathing mask for oxygen therapy in moderate category COVID-19 pneumonia: Randomized controlled trial Nazir et. al (2022) May 2022 IDENTIFIER: 10.7196/AJTCCM.2022.v28i1.206 **MODERATE**	Single-center, open-label, randomized controlled trial	India	120	**Inclusion Criteria:** -All COVID-19-positive patients of moderate category -Age ≥16 years -With informed consent for study inclusion **Exclusion criteria:** -Patients in the severe category of COVID-19 pneumonia -With Glasgow Coma Scale ≤12 -With primary pulmonary disease, tracheostomy, or any nasal/facial defect that could impede HFNC or NRBM	In HFNC, flow rate is set to 40 - 60 L/min, with fractional inspiratory oxygen concentration (FiO2) 0.8 - 1 adjusted to maintain oxygen saturation (SpO2) ≥96 - 99%. Achievement of the control of FiO2 was done by using an air oxygen blender (Oxymixture MP04200, Draeger, Germany).	In COT (NRFM), patients received oxygen therapy with NRBM used at a flow rate of 12 - 15 L/min with FiO2 0.8 - 1, adjusted to maintain SpO2 ≥96 - 99%. -FiO2 measured using a portable oxygen analyzer (MX 300, Teledyne Analytical Instruments, India).	**Primary Outcomes** -Progression-free survival without escalation of an oxygen delivery device. **Secondary Outcomes** -Partial pressure of arterial oxygen (PaO2) -The ratio PaO2/FiO2, RR, heart rate (HR), mean arterial pressure (MAP) -Number of patients requiring non-invasive ventilation (NIV) -Number of patients requiring endotracheal intubation -Time for de-escalation of oxygen therapy to lower FiO2 device -The time to progression to severe disease -Survival at day 28, -Patient satisfaction level.
High-flow nasal oxygen versus conventional oxygen therapy in patients with COVID-19 pneumonia and mild hypoxemia: a randomized controlled trial The COVID-HIGH trial Crimi et. al (2022) May 2022	investigator-initiated, multi-center, open-label, parallel-group, randomized controlled trial	Italy, Greece, Spain, Portugal, Poland, Turkey	364	**Inclusion Criteria:** -Age ≥18 years old; positive PCR test confirming SARS-CoV-2 infection -Clinical signs of acute respiratory infection -Radiological evidence of pneumonia -Peripheral oxygen saturation	HFNO was delivered by any available device able to deliver it. The initial flow rate was set at 40 L/min and increased as required up to 60 L/min, according to patient tolerance.	Oxygen was delivered preferably by a Venturi mask, but any other device was allowed, and a table of conversion for FiO2 was provided. FiO2 and oxygen flow were titrated to	**Primary Outcome** -Rate of escalation of respiratory support to CPAP, NIV or IMV within 28 days of randomization **Secondary Outcomes** -Rate of clinical recovery -Time to the escalation of respiratory support -Type of respiratory support as the first-line

IDENTIFIER: 10.1136/thoraxjnl-2022-218806 **MILD**				(SpO2) ≤92% or arterial partial pressure of oxygen to fraction of inspired oxygen (arterial oxygen tension (PaO2)/FiO2) ratio <300 in room air -Need for oxygen therapy according to clinical judgement, at screening. **Exclusion criteria:** -Respiratory rate ≥28 breaths/ min and/or severe dyspnea and/or use of accessory muscles; -PaO2/FiO2 ratio ≤200 -Need for immediate intubation, continuous positive airway pressure (CPAP) or non-invasive Ventilation (NIV) according to clinical judgement -Patients already on CPAP/NIV or HFNO at study screening -Septic shock -Evidence of multiorgan failure; -Glasgow Coma Scale <13 -Neuromuscular disease -Presence of partial pressure of arterial carbon dioxide (PaCO2) >45 mm Hg (if blood gas available) or history of chronic hypercapnia. -Patients already on long-term oxygen therapy and/ or home NIV/CPAP or with limitation of care based on patients' or physicians' decision -With the inability to comprehend the study content and give consent	The temperature was set from 37°C to 31°C according to patient comfort. A surgical mask was placed over the HFNO cannula. This is to maintain SpO2 between 92% and 96%.	maintain SpO2 between 92% and 96%.	escalation therapy by day 28, -Admission to ICU -Hospital and ICU length of stay -Dyspnea score (range, 0 (no dyspnea) to 10 (severe dyspnea) -Patient comfort score (Range, 0 (severe discomfort) to 10 (perfect comfort)) -SpO2/FiO2 ratio divided by Respiratory Rate (ROX index), National Early Warning Score 2 -Mortality at 28 and 60 days -In-hospital days free from CPAP/NIV/IMV -Oxygen free days -Treatment intolerance.

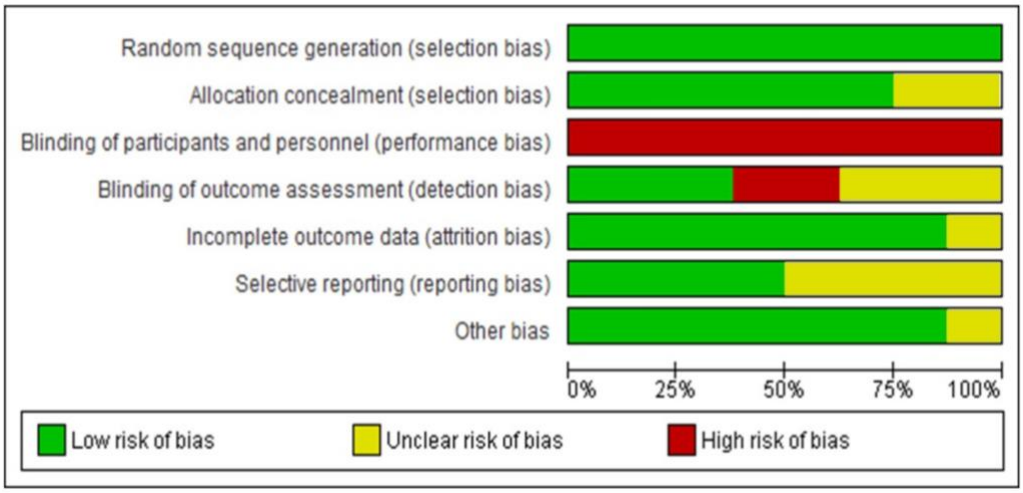
Effect of Helmet Noninvasive Ventilation VS High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients with COVID_19 and Moderate to Severe Hypoxemic Respiratory Failure The HENIVOT Randomized Clinical Trial Grieco et. al March 2021 IDENTIFIER: 10.1001/jama.2021.4682 **MODERATE TO SEVERE**	Investigator-initiated 2-group open label, multicenter randomized clinical trial	Italy	109	**Inclusion Criteria:** -All adult patients admitted in the intensive care units with acute hypoxemic respiratory failure and diagnosed with COVID-19 -PaO2/FiO2 equal or below 200 -Partial pressure of arterial carbon dioxide equal to or lower than 45 mmHg -Absence of history of chronic respiratory failure or moderate to severe cardiac insufficiency (NYHA >II or LV ejection fraction of <50%) **Exclusion Criteria:** -Acute exacerbation of chronic pulmonary disease -Kidney failure - Patients who had already received noninvasive ventilation or high-flow oxygen for more than 12 hours at the time of screening were excluded.	Non-invasive ventilation was delivered by a compressed gas-based ventilator connected to the helmet through a bi-tube circuit Initial pressure support between 10 and 12 cm H2) eventually increased to ensure a peak inspiratory flow of 100L//min Positive end expiratory pressure between 10 and 12 cm H2 and FiO2 titrated to obtain SpO2 between 92 and 98%	High flow nasal cannula for 48 hours Gas flow initially set at 60L/min and 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.	**Primary Outcome** -Number of days free of respirator support within 28 days after enrollment **Secondary outcome:** -Proportion of patients who required endotracheal intubation within 28 days from study enrollment -Number of days free of invasive mechanical ventilation at days 28 and 60 -In–intensive care unit mortality -In-hospital mortality -28-day mortality -60-day mortality -Intensive care unit length of stay -Safety end points
Comparison of High-Flow Nasal Cannula and Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure due to Severe COVID-19 Pneumonia Nair et al September 2021 IDENTIFIER: 10.4187/respcare.09130 **MODERATE TO SEVERE**	Single-center, prospective randomized controlled trial	India	109	**Inclusion Criteria:** -Adult patients 18-75 years old -Severe COVID-19 pneumonia presenting with fever, cough, respiratory distress with frequency >30 breaths/min and/or room air SpO2 <90% **Exclusion Criteria:** -Hemodynamic instability and requirement of high-dose vasopressor therapy -Pregnant -With the following conditions: COPD/chronic respiratory failure morbid obesity	NIV with either mask/helmet device connected to an ICU ventilator with the setting of Pressure support of 10-20 cmH2O adjusted to obtain an expired tidal volume of 7-10 mL/kg of PBW and PEEP 5-10 cm H2O and FiO2 0.5-1 titrated to target SpO2 >94%	HFNC with large bore binasal prongs and high flow heated humidifier device. Initial flow set up was at 50lpm and FiO2 of 1.0 The flow and FiO2 were adjusted between 30-60lpm and 0.5-1.0 to maintain SpO2 of >94%	**Primary Outcome:** -Early intubation rate -Proportion of subjects requiring invasive mechanical ventilation at 48 hours of ICU admission **Secondary Outcome** -Late intubation rate -Early improvement in oxygenation -In hospital mortality -Proportion of patients requiring awake prone positioning

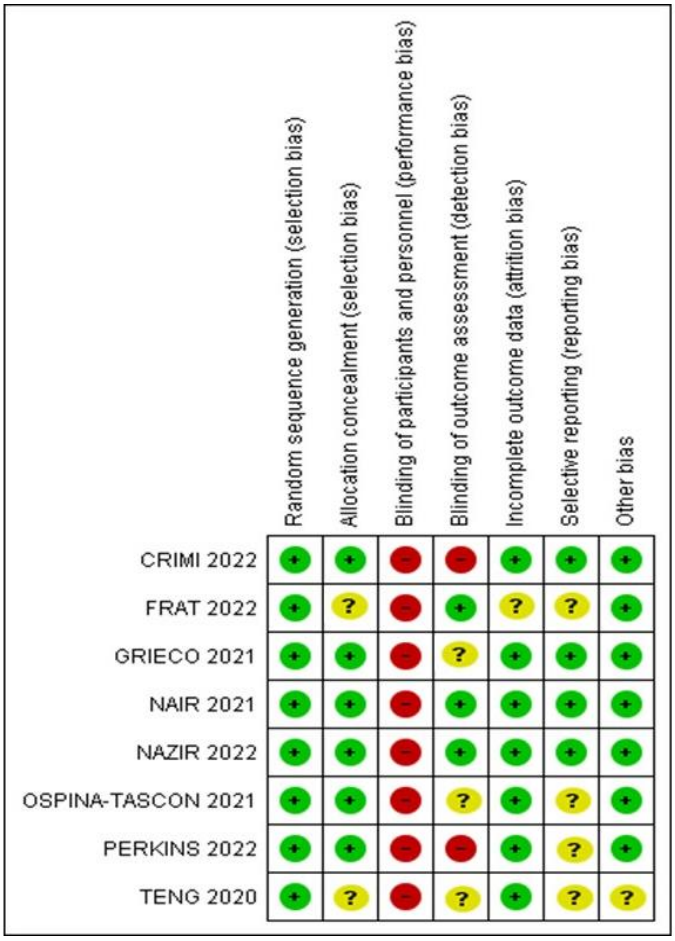
				-patients with urgent requirement of invasive mechanical ventilation due to severe hypoxia (SpO2 < 90% with frequency > 40 breaths/min for > 10 min) -patients with severe hemodynamic instability (mean arterial pressure < 65 mm Hg in spite of high-dose noradrenaline support) -With altered mentation (GCS<8) -Cardiac arrest			
An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19 The RECOVERY-RS Randomized Clinical Trial Perkins et. Al (2021) January 2022 IDENTIFIER: 10.1001/jama.2022.0028 **MODERATE TO SEVERE**	Parallel group, open-label, three-arm, adaptive, randomized controlled trial	London, United Kingdom	1259	**Inclusion Criteria:** -Adults >18 years old hospitalized with COVID-19 -Acute respiratory failure defined as SpO2 of <94% despite receiving a fraction of inspired oxygen of at least 0.4 -Deemed suitable for tracheal intubation of treatment escalation was required **Exclusion Criteria:** -Patients with an immediate (<1 hour) need for invasive mechanical ventilation, -Known pregnancy -Planned withdrawal of treatment	Participants randomized to High Flow Nasal Cannula started treatment as soon as possible and received heated humidified HFNO	**COT:** Conventional oxygen therapy (via face mask or nasal cannula) **CPAP:** The patients in the CPAP group received CPAP that did not permit the incorporation of any inspiratory positive airway pressure	**Primary Outcome** -Composite outcome of tracheal intubation or mortality within 30-days of randomization **Secondary Outcomes** -Incidence of tracheal intubation and mortality at 30 days -Time to tracheal intubation -Duration of invasive mechanical ventilation -Time to death -Mortality -Incidence of intensive care unit admission -Length of stay (ICU and hospital) ***post hoc analysis between HFNO and CPAP group done
The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia Teng et. al (2020) July 2020	Randomized controlled trial	Fuyang, China	22	**Inclusion Criteria:** -Age of the patients was >18 years -The patients met the diagnostic criteria for patients with severe COVID-19 **Exclusion criteria:**	HFNC oxygen therapy machine model: Optiflow PT101AZ Admitted to ICU Parameters: Temp 37˚C Flow Rate: 50LPM	Conventional Oxygen therapy: Admitted to ICU Nasal catheter or common mask (including venturi and oxygen storage mask)	**Primary Outcome** -Comparison of HR, RR and PaO2/FiO2 at each time point between 2 groups -Comparison of infection indexes between two groups before and after oxygen therapy -Comparison of length of ICU stay and total length of hospitalization between the two groups

IDENTIFIER: 10.1111/eci.13435 **MODERATE TO SEVERE**				-Partial pressure of carbon dioxide (PaCO2) >50 mmhg -previous chronic obstructive pulmonary disease or asthma -acute cardiogenic pulmonary edema or acute coronary syndrome -Glasgow coma scale <13.	Oxygen concentration 50% Parameters were adjusted according to blood oxygen saturation level (SpO2), blood gas and tolerance, maintaining SpO2 above 93 Duration of continuous treatment for all patients was >72 hours	Initial O2 absorption flow at 5lpm (adjusted according to the condition of SpO2 above 93%) Duration of treatment >72 hours *All patients were given Lopinavir/ritonavir tablets and interferon alpha as antiviral treatment for regulation of gastrointestinal flora and protection of organ function	
Effect of High-Flow Nasal Cannula Oxygen vs Standard Oxygen Therapy on Mortality in Patients With Respiratory Failure Due to COVID-19: The SOHO-COVID Randomized Clinical Trial Frat et. al (2022) September 2022 IDENTIFIER: 10.1001/jama.2022.15613 **MODERATE TO SEVERE**	Multicenter, open-label, parallel-group randomized clinical trial	France	711	**Inclusion Criteria:** - >18 years, admitted in ICU with an acute hypoxemic respiratory - pulmonary infiltrate; - PaO2:FiO2 ≤200 mmHg, - with informed consent from the patient or relatives - respiratory rate above 25 breaths/min **Exclusion criteria:** - PaCO2 > 45 mm Hg; - need for emergent intubation - hemodynamic instability - Glasgow coma scale equal to or below 12 - chronic lung disease including chronic – chronic lung disease with long term oxygen or ventilatory support; - cardiogenic pulmonary edema as main reason for acute respiratory failure;	Oxygen was continuously Delivered via large bore binasal prongs with gas flowof50L/min or more through a heated humidifier (MR850, Fisher &Paykel Healthcare). The fraction of oxygen was adjusted to maintain SpO2 between 92% and 96% (Optiflow or Airvo-2, Fisher & Paykel Healthcare; or an ICU ventilator with a high-flow oxygen therapy option). High-flow oxygen therapy was applied for at least 48 hours and was stopped and switched to standard oxygen therapy when the patient maintained SpO2 of at least 92% and a respiratory rate equal to or below25 per minute	Oxygen was continuously delivered through a nonrebreathing mask with oxygen flow set at 10 L/min or more, adjusted for oxygen saturation measured by pulse oximetry (SpO2) between 92% and 96% until recovery or intubation	**Primary Outcome** The proportion of patients who died within 28 days following randomization **Secondary Outcomes** - Intubation between randomization and D28 (failure of the oxygenation strategy), - Mortality in ICU, in hospital and at day 90, - Ventilation-free days at 28 days - Duration of ICU and hospital stay, - Complications during the ICU stay including septic shock, nosocomial pneumonia, cardiac arrhythmia, and cardiac arrest, - Dyspnea level using a 5-point Likert scale, - Comfort using a 100-mm visual-analogue scale, - Level of oxygenation assessed by arterial blood gas sample, - Sepsis-related Organ Failure Assessment (SOFA) score during the 48 hours after intubation, - Interval between the time when prespecified criteria of intubation are met and intubation

				- post-extubation respiratory failure within 7 days after extubation; - post-operative respiratory failure within 7 days after abdominal or cardiothoracic surgery; - do not intubate order; - Patients without any healthcare insurance scheme or not benefiting from it through a third party; - Persons under law protection, namely minors, pregnant or breastfeeding women, persons deprived of their liberty by a judicial or administrative decision .	with a FIO2 equal to or below 40%.		- Interval between treatment initiation and intubation

Appendix 4: Risk of Bias Assessment of Included Studies





Appendix 5: GRADE Evidence Profile

A. HFNC vs COT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Flow Nasal Cannula	Conventional Oxygen Therapy	Relative (95% CI)	Absolute (95% CI)		
28 days Mortality												
4	randomised trials	not serious	not serious	not serious	serious[a]	none	103/756 (13.6%)	108/711 (15.2%)	**RR 0.88** (0.69 to 1.12)	**18 fewer per 1,000** (from 47 fewer to 18 more)	⨁⨁⨁◯ Moderate	CRITICAL
Need for Mechanical Ventilation												
4	randomised trials	not serious	serious[b]	not serious	serious[a]	none	366/931 (39.3%)	400/882 (45.4%)	**RR 0.83** (0.67 to 1.02)	**77 fewer per 1,000** (from 150 fewer to 9 more)	⨁⨁◯◯ Low	CRITICAL
ICU Length of Stay												
5	randomised trials	serious[c]	not serious	not serious	serious[d]	none	1057	1007	-	MD **0.7 lower** (1.4 lower to 0)	⨁⨁◯◯ Low	CRITICAL
Hospital Length of Stay												
4	randomised trials	serious[c]	not serious	not serious	serious[d]	none	698	651	-	MD **0.72 lower** (2.65 lower to 1.2 higher)	⨁⨁◯◯ Low	CRITICAL
Ventilator Free Days												
3	randomised trials	serious[c]	not serious	not serious	serious[a]	none	638	636	-	MD **3.91 higher** (17.46 lower to 25.27 higher)	⨁⨁◯◯ Low	CRITICAL
Clinical Recovery												
3	randomised trials	serious[c]	not serious	not serious	serious[a]	none	259/341 (76.0%)	236/342 (69.0%)	**RR 1.07** (0.99 to 1.15)	**48 more per 1,000** (from 7 fewer to 104 more)	⨁⨁◯◯ Low	IMPORTANT
Heart Rate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Flow Nasal Cannula	Conventional Oxygen Therapy	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[c]	serious[e]	not serious	serious[d]	none	171	170	-	MD **1.52 higher** (1.91 lower to 4.95 higher)	⨁◯◯◯ Very low	IMPORTANT
Respiratory Rate												
3	randomised trials	serious[c]	serious[f]	not serious	serious[g]	none	171	170	-	MD **1.67 lower** (2.92 lower to 0.41 lower)	⨁◯◯◯ Very low	IMPORTANT
PaO2/FiO2 Ratio												
3	randomised trials	serious[c]	not serious	not serious	serious[g]	none	171	170	-	MD **34.6 higher** (32.4 higher to 36.8 higher)	⨁⨁◯◯ Low	IMPORTANT

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

Explanations

a. Risk estimates cross the line of no effect

b. substantial heterogeneity present (I2=72%) which may be due to real variation in the treatment effect or differences in the features of the population involved including, but not limited to, the severity of illness, age and gender. There is also presence of crossover between allocated treatment group.

c. Unclear risk of selection and performance bias in some of the included studies

d. Mean difference estimates cross line of no difference

e. substantial heterogeneity present (I2=78%) which may be due to variation in the treatment effect and differences in the features of the population included.

f. substantial heterogeneity present (I2=86%) which may be due to variation in the treatment effect and differences in the features of the population included.

g. low sample/event size

B. HFNC vs NIV (Helmet, CPAP)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Flow Nasal Cannula	Non Invasive Ventilation	Relative (95% CI)	Absolute (95% CI)		
28 days Mortality												
3	randomised trials	serious[a]	serious[b]	not serious	serious[c]	none	83/417 (19.9%)	75/371 (20.2%)	**RR 0.94** (0.60 to 1.48)	**12 fewer per 1,000** (from 81 fewer to 97 more)	⨁◯◯◯ Very low	CRITICAL
Need for Mechanical Ventilation												
3	randomised trials	serious[a]	serious[d]	not serious	serious[c]	none	167/416 (40.1%)	123/370 (33.2%)	**RR 1.21** (1.00 to 1.46)	**50 fewer per 1,000** (from 250 fewer to 150 more)	⨁◯◯◯ Very low	CRITICAL
Hospital Length of Stay												
2	randomised trials	serious[a]	not serious	not serious	serious[c]	none	110	108	-	MD **0.58 higher** (36.27 lower to 37.42 higher)	⨁⨁◯◯ Low	CRITICAL
Ventilator Free Days												
2	randomised trials	serious[a]	not serious	not serious	serious[c]	none	110	108	-	MD **0.94 lower** (27.04 lower to 25.16 higher)	⨁⨁◯◯ Low	CRITICAL

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

Explanations

a. Unclear to high-risk selection and performance bias

b. substantial heterogeneity present (I2=52%) which may be due to variation in the treatment effect and differences in the features of the population included.

c. Risk estimates cross line of no effect

d. substantial heterogeneity present (I2=81%) which may be due to variation in the treatment effect and differences in the features of the population included

Appendix 6: Forest Plots

A. HFNC vs COT

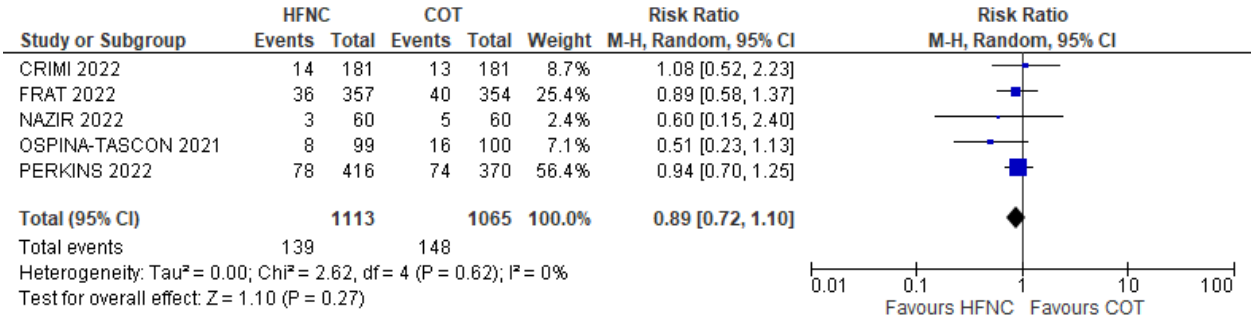


Figure 1. Forest plot for Mortality at 28 Days

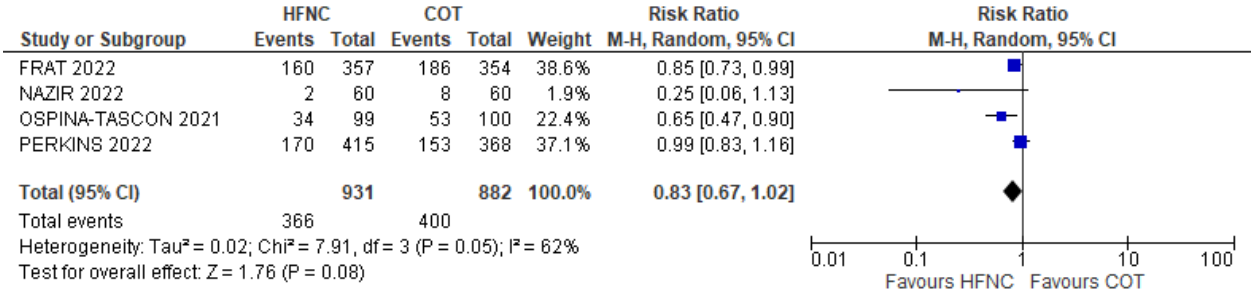


Figure 2. Forest plot for Need for Mechanical Ventilation

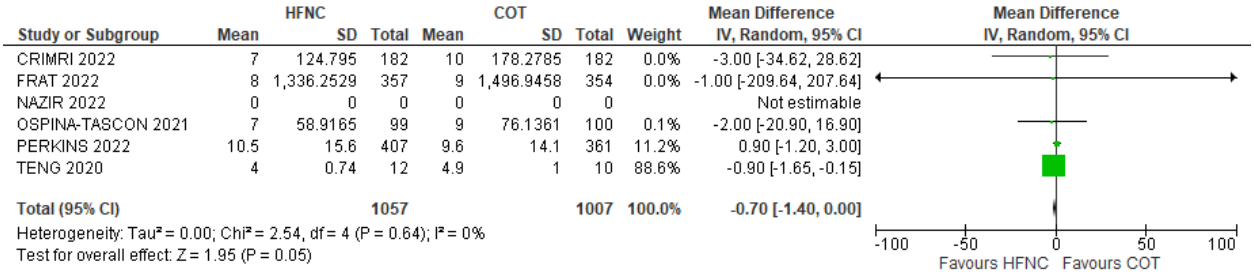


Figure 3. Forest plot for ICU Length of Stay

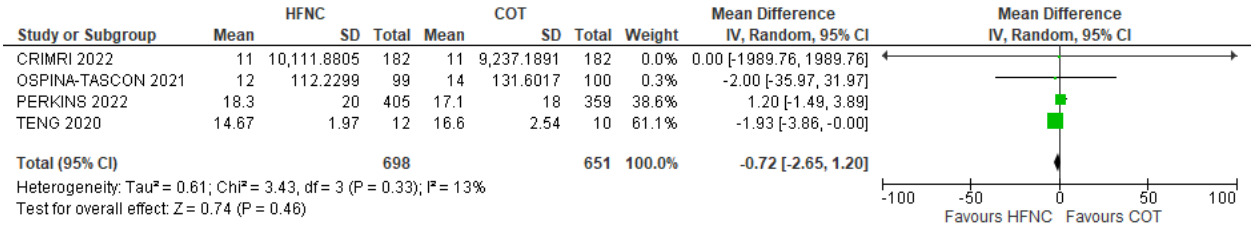


Figure 4. Forest plot for Hospital Length of Stay

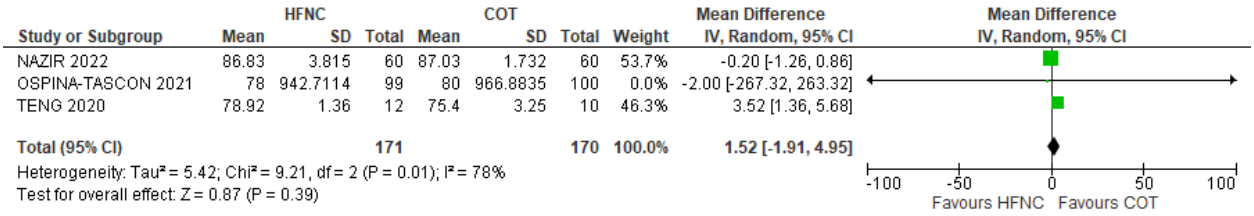


Figure 5. Forest plot for Comparison of Heart Rate between groups

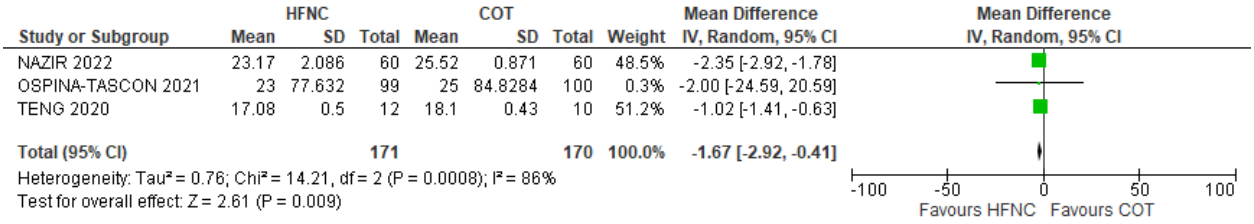


Figure 6. Forest plot for Comparison of Respiratory Rate between groups

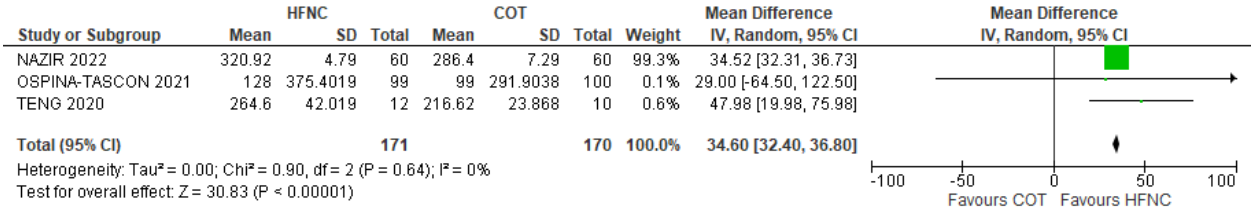


Figure 7. Forest plot for Comparison of PaO_2/FiO_2 between groups

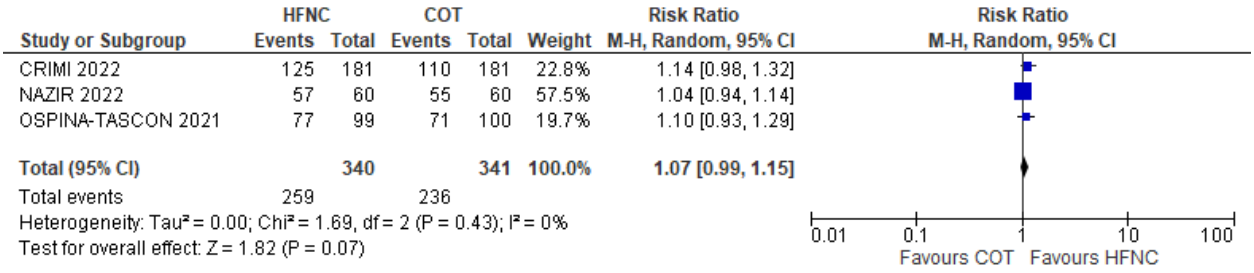


Figure 8. Forest plot for Clinical Recovery

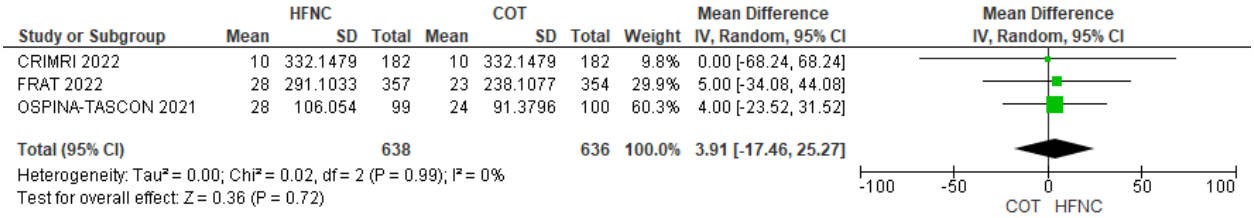


Figure 9. Forest plot for Ventilator Free Days

B. HFNC vs NIV

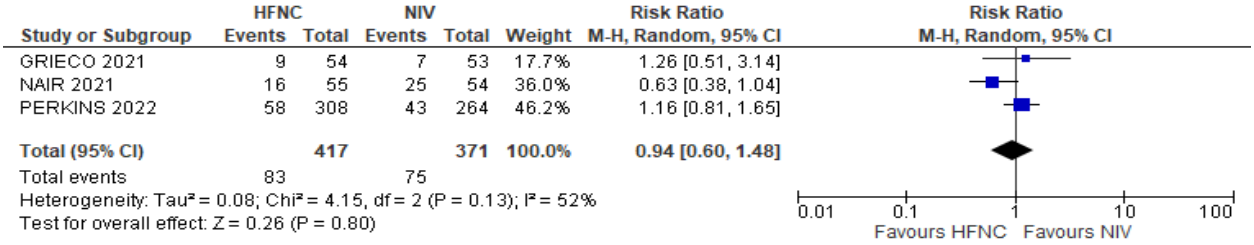


Figure 10. Forest plot for Mortality at 28 Days

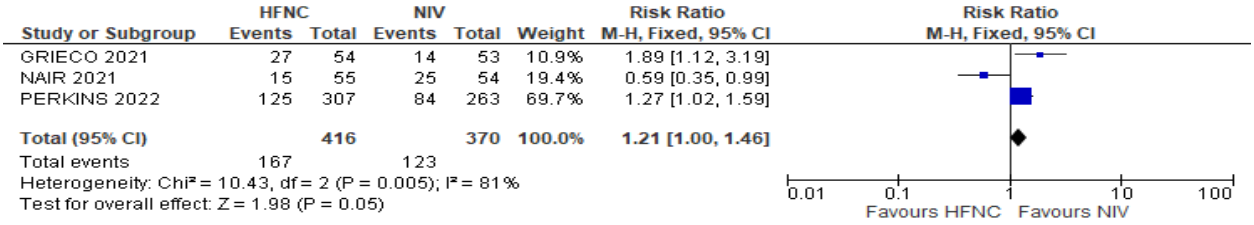


Figure 11. Forest plot for Need for Mechanical Ventilation

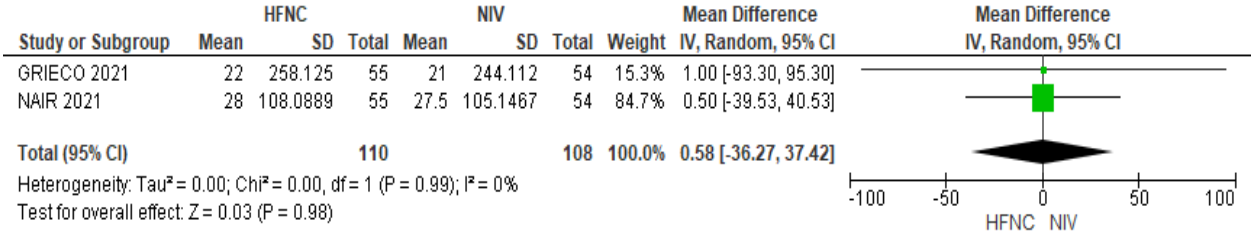


Figure 12. Forest plot for Hospital Length of Stay

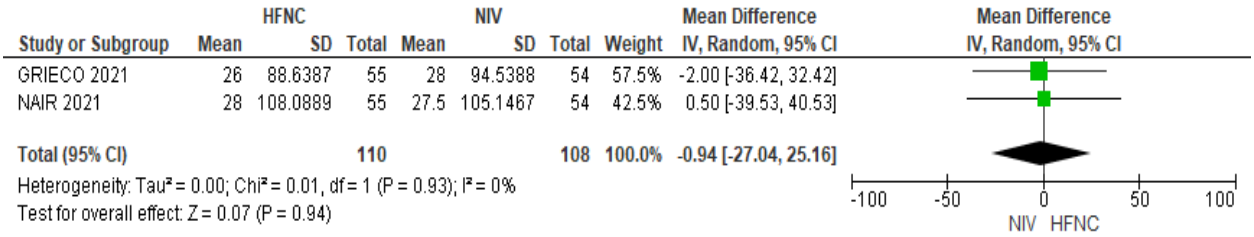


Figure 13. Forest plot for Ventilator Free Days

Appendix 7: Ongoing Studies (n=8)

Title Identifier Expected Completion Date	Intervention	Comparator/ Control	Patients/Population Recruited	Outcomes
Comparison of High Flow Nasal Cannula (HFNC), Face-mask Non-Invasive Ventilation (NIV) & Helmet NIV in COVID-19 ARDS Patients NCT04715243 Estimated Study completion date: December 30, 2021	Intervention 1: high flow nasal cannula Intervention 2: helmet NIV	Face-mask NIV	Inclusion Criteria: >18 years of age confirmed COVID-19 Within 48 hours of presentation in the emergency department, high dependency area or intensive care unit (ICU) ARDS according to Berlin definition (P/F < 300) or O2 saturation < 90% or RR > 30/min) in room air Standard oxygen therapy at flow rate < 15L/min x 60 minutes	Primary Outcome Measures: 1. Rate of endotracheal intubation [Time Frame: within the study period with an average of one month.] Secondary Outcome Measures: 1. Hospital mortality [Time Frame: 90 days from the hospital mortality.] 2. Hospital length of stay [Time Frame: Throughout the study completion. An average of 90 days.] 3. Ventilator free days [Time Frame: Throughout the study completion. An average of 90 days.]
A randomized controlled trial of high flow nasal oxygen versus non rebreathing oxygen face mask therapy in acute hypoxemic respiratory failure CTRI/2020/12/029803 *Not yet recruiting*	High flow nasal cannula	Conventional oxygen therapy	All adult patients aged 18 years and above diagnosed as acute hypoxemic respiratory failure with covid positive status	Treatment failure
Randomized Controlled Trial to evaluate the effectiveness of HFNC and standard non-rebreathing mask for oxygen therapy in moderate category COVID 19 pneumonia CTRI/2021/01/030829 *Not yet recruiting*	High flow nasal cannula	Standard non-rebreathing mask	Adult patients with COVID-19 pneumonia	Time to progression to severe disease PaO2/FiO2 ratio, patient tolerance & acceptability will be assessed and Length of hospital stay will be recorded
Comparison use of High Flow Nasal Cannula and Non-invasive ventilation in patients with Covid-19: A randomized comparative study CTRI/2020/11/029356 *Not yet recruiting*	High flow nasal cannula vs NIV	High flow nasal cannula vs NIV	Patients with COVID-19 rtPCR positive who requires HFNO and NIV as first line therapy	Reduction in respiratory distress signs like decrease in respiratory rate and increase in saturation SpO2 90%. Improvement in hemodynamic stability such as Heart rate, respiratory rate and blood pressure improvement in chest x-ray/High Resolution Computerized Tomography. ICU stay and outcome of HFNO and NIV.

				Incidence of failed HFNO and NIV who needs intubation
Efficacy of awake prone positioning with high flow nasal cannula versus prone positioning with non-rebreathing mask in COVID-19 patients. A prospective comparative study CTRI/2020/12/029587 *Not yet recruiting*	Awake prone positioning with high flow nasal cannula	Awake prone positioning with non-rebreathing mask	Adult Confirmed COIVD19 positive patients admitted to ICU for acute hypoxemic respiratory failure	Intubation rates Intubation-free ICU stay Time to require NIV
Evaluation of the effectiveness of high flow nasal cannula (HFNC) oxygen delivery in comparison with non-invasive ventilation (NIV) in patients with COVID-19 IRCT20160516027929N8 *Recruitment status completed, but no available results*	HFNC	NIV	Adults with COVID-19 pneumonia	Partial pressure of carbon dioxide. Timepoint: Before the intervention, 24 hours after the intervention and 48 hours after the intervention. Oxygen saturation
High Flow Nasal Oxygen Versus Continuous Positive Airway Pressure Helmet Evaluation: A Randomized Crossover Trial in COVID-19 Pneumonia *COVIDNOCHE Trial* NCT04381923 Estimated study completion: December 2022	HFNC	Hemet CPAP	Inclusion Criteria: Adult patients with confirmed COVID-19 with an Sp02 < 92% on ≥ 6 liters NC admitted to a Penn Medicine advanced respiratory unit. An advanced respiratory unit is a unit capable of non-invasive respiratory support such as an ICU or intermediate care unit	Primary Outcome Measures: 1. Ventilator-Free Days (VFD) [Time Frame: 28 days] Secondary Outcome Measures: 1. ICU and Hospital Length of Stay [Time Frame: 28 days] Days spent in the ICU and hospital after time of enrollment 2. Intubation [Time Frame: 28 days] Incidence and time to intubation in days after the time of enrollment 3. Renal Replacement Therapy (RRT) [Time Frame: 28 days] Incidence of RRT after the time of enrollment 4. Mortality [Time Frame: 28 days, 90 days] Death from any cause during after the time of enrollment
Comparison of efficacy of High Flow Nasal Cannula with Continuous Positive Airway Pressure in prevention of Invasive mechanical ventilation in COVID 19 patients with	HFNC	NIV	Inclusion criteria: All COVID -19 positive patients (by RT-PCR) with paO2/Fio2 (P/F) 150 to 250, with good	Primary outcome: 1. To compare the efficacy of High Flow Nasal Cannula and Non-Invasive Ventilation -Continuous Positive Airway Pressure in reducing need for invasive

acute respiratory distress syndrome in Critical Care Unit- A Randomized Control Study - COVID HFNC CTRI/2021/04/032501 Not yet recruiting			sensorium, stable hemodynamics and pH > 7.2	mechanical ventilation in patients with ARDS in COVID-19. Timepoint: 24 hours Secondary outcome: 1. Ability of ROX index to identify COVID 19 patients on HFNC requiring invasive mechanical ventilation. Timepoint: 24 hours 2. Ability to alleviate dyspnea as assessed by modified Borg scale. Timepoint: 24 hours 3. Patient's compliance to therapy - comfort / noise level, ability to prone Timepoint: 24 hours