Non-invasive ventilation and heated humidified high-flow oxygen therapies for severe COVID-19: **Rapid Evidence Report**

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Executive Summary

The Coronavirus Disease 2019 (COVID-19) pandemic has placed enormous stress on acute care systems around the world. Mild disease in adults results in influenza-like illness (fever, chills, cough, and sore throat), while severe disease results in pneumonia and acute respiratory distress that requires hospitalization and in the worst cases, intensive care with mechanical ventilation. Based on experience with non-COVID respiratory disease, patients with severe disease early in the pandemic received mechanical ventilation as soon as possible; however, as the research advanced, it became clearer that early intubation was not necessarily the best treatment for COVID-19 pneumonia and acute respiratory distress. This review was commissioned by the Respiratory Health Section of the Medicine Strategic Clinical Network (MSCN) to synthesize current evidence on non-invasive ventilation (NIV) and heated humidified high-flow oxygen (HHHFO) for severe COVID-19 to update Alberta Health Services (AHS) provincial guidance for adults hospitalized with COVID-19.

This review was initially proposed as two separate reviews; accordingly, two sets of research questions and PICOS were designed. The questions to be addressed are below.

Heated Humidified High-Flow Oxygen and COVID

1. Does HHHFO have clinical benefit for adult COVID-19 patients, and for how long, before the patient requires mechanical ventilation?
2. What are the characteristics of adult COVID-19 patients who may benefit from HHHFO? (Are there differences between patient subgroups associated with greater or worse outcomes)
3. What signs or symptoms indicate that an adult COVID-19 patient requires mechanical ventilation instead of receiving HHHFO?

Non-invasive Ventilation for Acute COVID-related Hypoxemia or Respiratory Failure

1. What is the clinical effectiveness of NIV (i.e., CPAP or Bilevel PAP), compared to HHHFO or intubation, for adult inpatients with acute COVID-related hypoxemia/respiratory failure?
2. Under what clinical conditions and in what inpatient setting is NIV more appropriate than HHHFO or intubation for managing adults with acute COVID-related hypoxemia/respiratory failure?
3. What are the risks associated with NIV for adult inpatients with acute COVID-related hypoxemia/respiratory failure compared to HHHFO or intubation?

The literature search was conducted by Knowledge Resource Services (KRS) within the Knowledge Management Department of Alberta Health Services. As this review was initially conceptualized as separate reviews, three searches were conducted with the following foci: HHHFO and COVID-19; ventilation and COVID-19; and NIV and COVID-19. KRS searched databases for English language papers published from 2020 to 2021 and included: Ovid Medline, Embase, and CINAHL. Guidelines and grey literature were limited to the United Kingdom, Australia, New Zealand, United States, Canada, European Union, and the World Health Organization. 933 articles were identified by KRS with references and abstracts provided for further review. Following two rounds of screening according to pre-determined inclusion or exclusion criteria, 15 articles from the literature search were selected for inclusion. Hand searching identified one additional primary study and four guidelines. In total, 21 articles were included in the final narrative synthesis.

This review was limited by several factors that must be considered when assessing the findings. First, this is a rapid review. The search was thorough, but not systematic. In addition, the search was limited to literature published in English in the past 2 years. For these reasons, it is possible that relevant studies were not captured in the database search.

As with most reviews of COVID-19-related evidence, this review is limited by the lack of controlled trial evidence. Observational studies cannot show causation, only association; thus, it is difficult to determine if the intervention being studied truly has clinical benefit or if benefit is due to the characteristics of the patient. These studies also suffer from the rapid pace of COVID-19 research, where studies are haphazardly designed with little attention paid to limiting bias. As a result, the studies included in this review are at high risk of bias from confounding.

With respect to the body of evidence, the terminology around high-flow oxygen is not standardized, which makes searching for grey literature challenging. The most common terms include “high flow nasal cannula”, “high flow nasal oxygen”, “heated humidified high-flow nasal cannula”, “heated humidified high-flow oxygen”, and “high-flow oxygen”. It is therefore difficult to determine if each term refers to the same systems and mode of therapy.

Based on the evidence presented in the synthesis above, the following conclusions can be made:

- The body of evidence on this topic is estimated to be of low quality. It is largely cohort studies at high risk of confounding, and guidance based on this review should acknowledge this limitation.
- No peer-reviewed RCTs were identified to address the research questions specifically relating to CPAP and Bilevel PAP as therapy for COVID-19.
- Guidelines from the WHO, Europe, UK, USA, and Australia unanimously recommend using non-invasive oxygen therapy (such as high-flow nasal cannula, CPAP, or Bilevel PAP) in hypoxemic patients requiring oxygen supplementation but for whom invasive mechanical ventilation is not yet indicated.
- The principal risk to patients arising from non-invasive oxygen supplementation in COVID-19 appears to be delayed intubation, which can be mitigated by close monitoring and not trying to rescue respiratory function with additional non-invasive therapy or positioning once therapy failure has been determined.
- One RCT found that early oxygen therapy via high-flow nasal cannula (HHHFO) resulted in significantly better respiratory rate, heart rate, and PaO_2/FiO_2 at 6 hours post treatment initiation compared to conventional oxygen therapy. Observational studies support this finding and show that non-invasive ventilation can reduce the ICU length of stay and ventilator-free days, but is not necessarily associated with a decrease in mortality
- Benefit from non-invasive therapies is associated with early intervention, rather than with patient characteristics. The need for intubation is influenced by the patient’s physiological and biochemical characteristics. NIV as a therapy is not clearly associated with reduced need for mechanical ventilation.
- No direct evidence was identified that described best practices for identifying when to move a patient to mechanical ventilation from non-invasive ventilation. The ROX index score is a valid prognostic measure of HHHFO success or failure. ROX index values below 5.5 that do not increase over time (up to 16 hours after start of HHHFO therapy, or limited response within the first 6 hours) are strongly associated with increased risk of intubation, while patients who did not require intubation had a ROX index value above 5.5 at baseline that increased as therapy continued.

Background

The Coronavirus Disease 2019 (COVID-19) pandemic has placed enormous stress on acute care systems around the world. Mild disease in adults results in influenza-like illness (fever, chills, cough, and sore throat), while severe disease results in pneumonia and acute respiratory distress that requires hospitalization and in the worst cases, intensive care with mechanical ventilation (Alberta Health, 2021). Due to the novelty of the disease, the clinical management of COVID-19 patients has evolved rapidly as research becomes available and the natural history of the disease becomes clearer.

Based on experience with non-COVID respiratory disease, patients with severe disease early in the pandemic received mechanical ventilation as soon as possible; however, as the research advanced, it became clearer that early intubation was not necessarily the best treatment for COVID-19 pneumonia and acute respiratory distress (AHS Scientific Advisory Group, 2020). This review was commissioned by the Respiratory Health Section of the Medicine Strategic Clinical Network (MSCN) to synthesize current evidence on non-invasive ventilation (NIV) and heated humidified high-flow oxygen (HHHFO) for severe COVID-19 to update Alberta Health Services (AHS) provincial guidance for adults hospitalized with COVID-19.

Research Questions

The following research questions were formulated based on the PICO framework. These questions were used as a basis for the literature search. Initially, these two topics were proposed as two separate reviews; upon discussions with the requestor and with the manager of the Respiratory Health Section of the MSCN, it was agreed that it would be useful to package the two reviews together as they address similar questions and would use very similar searches. The research questions and PICOS frameworks are included below.

Section 1: Heated Humidified High-Flow Oxygen and COVID

1. Does HHHFO have clinical benefit for adult COVID-19 patients, and for how long, before the patient requires mechanical ventilation?
2. What are the characteristics of adult COVID-19 patients who may benefit from HHHFO? (Are there differences between patient subgroups associated with greater or worse outcomes)
3. What signs or symptoms indicate that an adult COVID-19 patient requires mechanical ventilation instead of receiving HHHFO?

Population	Adult inpatients (> 18) with COVID-induced hypoxemia or COVID-induced hypoxemic respiratory failure
Intervention	Use of heated humidified high-flow oxygen therapy (i.e. OptiFlow, AIRVO, Vapotherm)
Comparator	Mechanical ventilation earlier in the care pathway (any therapy prior to intubation)
Outcomes	Any outcomes are of value, especially prevention of intubation and/or resolution of hypoxemia
Study Types	Any - all experimental and quasi-experimental (RCTs, non randomized trials, before and after, time series, etc), observational (cohort and case control) as well as secondary (systematic reviews and meta analyses), guidelines

Section 2: Non-invasive Ventilation for Acute COVID-related Hypoxemia or Respiratory Failure

1. What is the clinical effectiveness of NIV (i.e., CPAP or Bilevel PAP), compared to HHHFO or intubation, for adult inpatients with acute COVID-related hypoxemia/respiratory failure?
2. Under what clinical conditions and in what inpatient setting is NIV more appropriate than HHHFO or intubation for managing adults with acute COVID-related hypoxemia/respiratory failure?
3. What are the risks associated with NIV for adult inpatients with acute COVID-related hypoxemia/respiratory failure compared to HHHFO or intubation?

Population	Adult inpatients (stratify for medicine vs. intensive care units)
Intervention	Use of non-invasive ventilation (CPAP or Bilevel PAP) for management of COVID-related hypoxemia or respiratory failure
Comparator	Compared to HHHFO and/or intubation
Outcomes	Time to recovery, morbidity (e.g., work of or difficulty breathing), mortality
Study Types	Randomized controlled trials Grey literature: guidelines; position statements; recommendations; guidance documents

Literature Search Strategy

The literature search was conducted by Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. As this review was initially conceptualized as separate reviews, three searches were conducted with the following foci: HHHFO and COVID-19; ventilation and COVID-10; and NIV and COVID-19. A brief grey literature search was conducted by the librarian and was supplemented with hand-searching by the analyst.

KRS searched databases for English language papers published from 2020 to 2021 and included: Ovid Medline, Embase, and CINAHL. Guidelines and grey literature were limited to the United Kingdom, Australia, New Zealand, United States, Canada, European Union, and the World Health Organization. The full search strategy is included in the appendix of this report. Briefly, the following combinations of concepts were used to design the search:

- KRS filter for COVID-19
- Clinical outcomes (eg. length of stay, disease progression, risk assessment)
- Respiratory support (eg. mechanical ventilation, CPAP, BiPAP, non-invasive ventilation, high-flow oxygen)

Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Tables 1 and 2 below. 933 articles were identified by KRS with references and abstracts provided for further review. 738 articles were excluded from the review at the title and abstract stage. A further 180 (165 after de-duplication) were excluded after full-text review in accordance with the inclusion/exclusion criteria stated below. 15 articles from the literature search were selected for inclusion. Hand searching identified one additional primary study and four guidelines. In total, 21 articles were included in the final narrative synthesis. A flow diagram of identified studies is included in Figure 1.

Inclusion and Exclusion Criteria

The Analyst screened titles and abstracts of the search output and evaluated the selected full-text publications for final article selection using predefined inclusion and exclusion criteria. The criteria are defined below:

Table 1. Inclusion and exclusion criteria for Section 1 (HHHFO for COVID-19)

Inclusion Criteria	Exclusion Criteria
- Adult inpatients (> 18) with COVID-induced hypoxemia or COVID-induced hypoxemic respiratory failure - Use of heated humidified high flow oxygen therapy (i.e. OptiFlow, AIRVO, Vapotherm - Any outcomes - Any study type - all experimental and quasi-experimental (RCTs, non randomized trials, before and after, time series, etc), observational (cohort and case control) as well as secondary (systematic reviews and meta analyses), guidelines	- Primary goal of study is medication trial - Lab study or non-human study - Virus other than SARS-CoV-2 - Ambulatory care - ECMO - Descriptive study only - Case report or case series ≤10 - Modelling study - Commentary, narrative review, editorial, conference abstract

Table 2. Inclusion and exclusion criteria for Section 2 (NIV for Acute COVID-related Hypoxemia or Respiratory Failure)

Inclusion criteria	Exclusion criteria
Peer-reviewed data and grey literature (see below) published after August 1, 2020	Pre-prints; published before Aug 1, 2020
Adult inpatients (> 18) with COVID-19 and COVID-induced hypoxemia or hypoxemic respiratory failure	Not adults; not inpatient setting; non-COVID patients with hypoxemia or hypoxemic respiratory failure
Intervention: Non-invasive ventilation: CPAP or Bilevel PAP	Other oxygen therapy as intervention or comparator
Comparators: HHHFO or intubation	
Outcomes: time to recovery, morbidity, mortality	
Randomized controlled trials Grey literature: guidelines; position statements; recommendations; guidance documents	Any other non-randomized experimental or observational study designs; Commentaries, Letters, Opinions, Animal Studies, modelling study, non-randomized evaluation study

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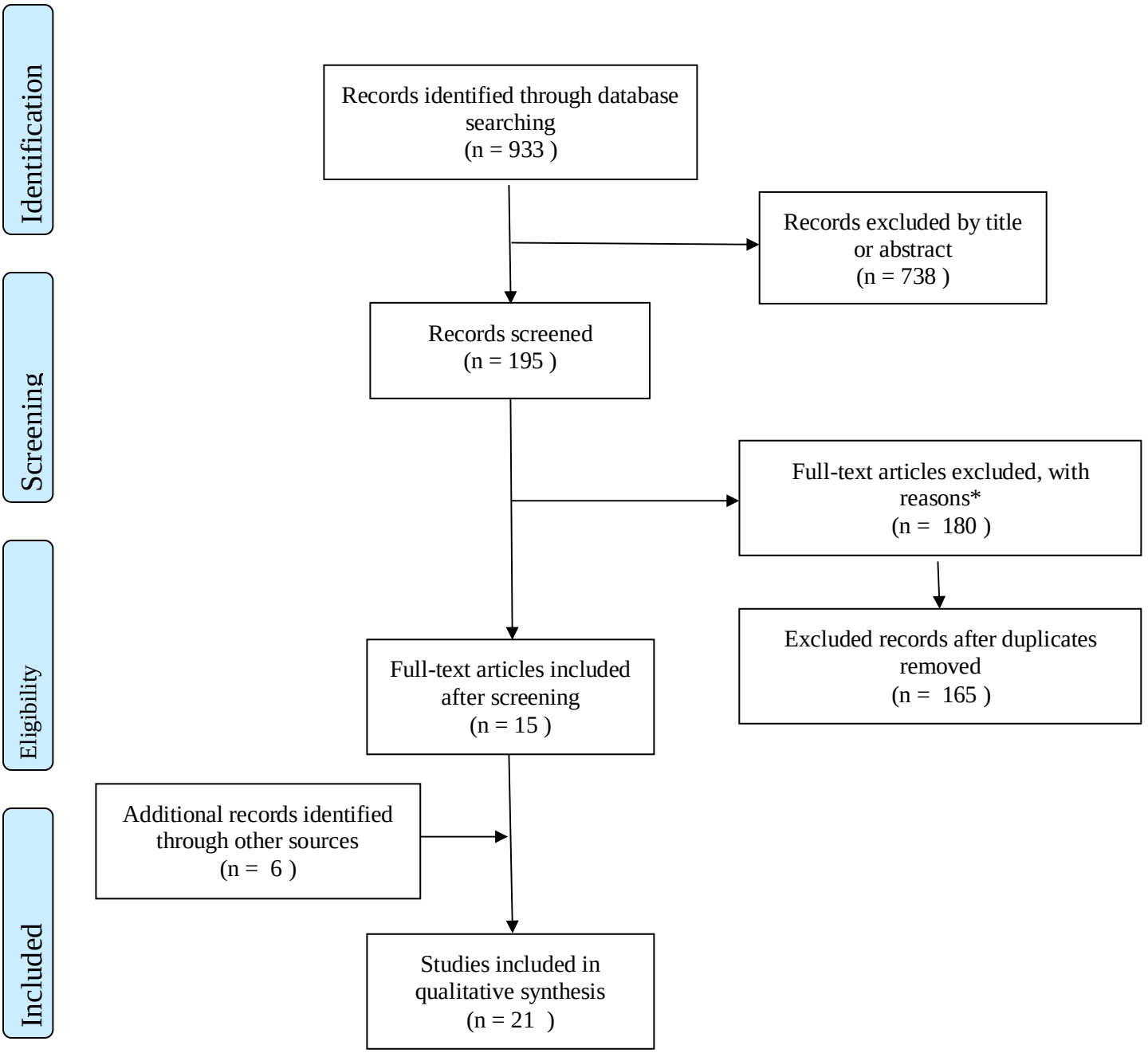
Figure 1. PRISMA[1] Flow diagram of the identified studies. 21 articles were included in this rapid review.



[1] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses:* The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Evidence Summary

The database search yielded 933 citations published between 2020 and 2021. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. After both rounds of screening, 15 articles were retained for inclusion and six articles were identified for inclusion by hand-searching.

Although no formal quality appraisal was conducted for this review, the evidence for this topic can be estimated to be of low quality. As COVID-19 is a novel disease, clinical studies are often designed haphazardly and performed quickly. Further, the body of knowledge regarding management and treatment has evolved over time. From the evidence identified here, the effect of adjunctive steroid and antiviral treatment and prone positioning to supplement to non-invasive oxygen therapy in severe COVID-19 is unclear. Clinical trials of medications for COVID-19 were excluded from this review, and prone positioning has been previously reviewed by the AHS Scientific Advisory Group on COVID-19. In the evidence included here, patients are receiving the standard of care as determined by the medical institution providing care according to the evidence available during the study period.

As described above, the two topics addressed here were originally conceptualized as two separate reviews; accordingly, they have separate PICOS charts and inclusion/exclusion criteria. Importantly, different study types were accepted for the two topics: any study type was accepted for the research questions on HHHFO, while only RCTs and guidelines were accepted for the research questions on CPAP and Bilevel PAP.

Grey literature for non-invasive respiratory therapies

Sixteen pieces of grey literature were retrieved by the librarian for this review. Fifteen articles were excluded, and an additional five guidelines were identified by hand searching, for a total of six included guidelines in the narrative synthesis. The extracted sections from each guideline are included below in Table 4.

The guidelines retrieved from the World Health Organization (WHO) (2021), National Institutes of Health (2021) (USA), National Institute for Health and Care Excellence (NICE) (2021) (UK), National COVID-19 Clinical Evidence Taskforce (2021) (Australia), European Respiratory Society (Chalmers et al., 2021), and British Thoracic Society (Messer et al., 2021) unanimously recommend using non-invasive ventilation and/or heated humidified high-flow oxygen therapy in hypoxemic patients requiring oxygen supplementation but for whom invasive mechanical ventilation is not yet indicated (i.e. the inability to maintain oxygen saturations ≥94% on an inspired oxygen <40% (Messer et al., 2021)). Patients with COVID-19 hypoxemia should receive oxygen therapy to achieve a target saturation (SpO_2) ≥ 92% (National COVID-19 Clinical Evidence Taskforce, 2021; Messer et al., 2021; WHO, 2021; National Institutes of Health, 2021). None of the identified guidelines suggested a sequence for HHHFO or CPAP/Bilevel PAP; however, the National Institutes of Health (2021) expressed a preference for high-flow nasal cannula oxygen (i.e. HHHFO) over positive pressure ventilation.

The principal risk to patients arising from use of non-invasive respiratory therapies in COVID-19 appears to be delayed intubation. Most of the guidelines made a specific recommendation that mechanical ventilation should be initiated without delay (i.e. without attempting to rescue respiratory function with less-invasive therapies or positioning) and should be achieved by closely monitoring the patient while they are receiving non-invasive respiratory support (Chalmers et al., 2021; National COVID-19 Clinical Evidence Taskforce, 2021; WHO, 2021; NICE, 2021). The British Thoracic Society describes non-invasive respiratory support failure as: limited initial response within 6h, lack of improvement within 3 days, unchanged/increasing work of breathing, and not tolerating CPAP/NIV breaks (Messer et al., 2021).

The guidance also noted the potential for COVID-19 transmission to hospital staff because of the aerosol-generating nature of some non-invasive ventilation strategies (Chalmers et al., 2021; National COVID-19 Clinical Evidence Taskforce, 2021). Appropriate personal protective equipment (PPE) should be worn by healthcare providers according to local guidance and practice.

Primary literature for non-invasive respiratory therapies

Heated Humidified High-Flow Oxygen and COVID

Fourteen articles were identified that met the inclusion criteria for the research questions regarding HHHFO treatment for COVID-19. One study was an RCT (Teng et al., 2020) and the remaining thirteen were cohort studies (7 retrospective, 6 prospective). The evidence from each article is included in Table 3 below.

Does HHHFO have clinical benefit for adult COVID-19 patients, and for how long, before the patient requires mechanical ventilation?

The RCT identified in the literature search showed that early oxygen therapy via high-flow nasal cannula (HHHFO) resulted in significantly better respiratory rate (RR), heart rate (HR) and PaO_2/FiO_2 at 6 hours post treatment initiation compared to conventional oxygen therapy (Teng et al., 2020). Despite no differences in patient characteristics at baseline, patients who were treated with HHHFO had a higher PaO_2/FiO_2 and lower respiratory rate at 24 and 72 hours compared to patients receiving conventional oxygen therapy (Teng et al., 2020).

One cohort study was identified that compared patients admitted to the intensive care unit (ICU) who received either high-flow nasal oxygen (HHHFO) within the first 24 hours or early invasive mechanical ventilation within the first 24 hours (Mellado-Artigas et al, 2021). HHHFO was associated with an increase in ventilator-free days (mean difference 8.0 days; 95% CI 4.4 to 11.7 days), a reduction in ICU length of stay (mean difference -8.2 days; 95% CI -12.7 to -3.6 days) and a 38% intubation rate (compared to an expected 100% rate in the comparator group) (Mellado-Artigas et al., 2021). In a study of elderly patients with confirmed COVID-19, those who received early HHHFO treatment (200 mmHg < $PO_2/FiO_2 \leq 300$ mmHg) instead of conventional oxygen therapy were less likely to develop secondary infection pneumonia, or severe respiratory distress and were less likely to have an ICU stay longer than 7 days (Deng et al., 2021)

Like Mellando-Artigas (2021), Wendel Garcia et al. (2021), in an international patient cohort, found that non-invasive ventilation (NIV) was independently associated with higher overall ICU mortality (adjusted HR 2.67, 95% CI [1.14–6.25]) as well as with an increased ICU mortality rate (adjusted HR 2.96, 95% CI [1.07–8.23]) and a prolonged length of ICU stay (adjusted HR 0.57, 95% CI [0.33–0.97]) in patients failing NIV and requiring IMV. This was hypothesized by the authors to be due to longer periods of harmful spontaneous breathing and possibly delaying mechanical ventilation (Wendel Garcia et al., 2021).

No difference was observed in all-cause in-hospital mortality between groups (OR 0.64; 95% CI 0.25 to 1.64) (Mellado-Artigas et al., 2021). Likewise, the prospective cohort study by Franco et al. (2020) also found that HNFC had no significant reduction in risk of 30-day mortality, intubation, or length of hospital stay compared to other NIV modes. Conversely, another study by Palacios Chavarria et al. (2021) found that the HFNC success rate, defined as patients who did not require IMV, was 71.4% (n = 270; 95% CI 66.6–75.8) compared with 28.6% (n = 108; 95% CI 24.2–33.4) of patients who required IMV. Panadero et al. (2020) and Patel et al. (2020) also report higher mortality in patient groups requiring intubation; however, this likely reflects the severity of illness in this patient group, not an effect of the non-invasive treatment.

What are the characteristics of adult COVID-19 patients who may benefit from HHHFO? (i.e. Are there differences between patient subgroups associated with greater or worse outcomes)

Many of the cohort studies included in this review differentiated their patient groups as HFNO success and HFNO failure. Because of the study designs identified in the evidence, it is very difficult to determine if patients who are successful on high-flow therapy due to the therapy itself or because they had less severe disease. Beduneau (2021) notes that intubated patients more frequently had diabetes; however, this does not suggest that they do not benefit from HHHFO.

The RCT by Teng (2020) suggests that initiating therapy before COVID-19 pneumonia becomes too severe might be the determining factor of NIV success, as there was no difference in age, gender, onset of symptoms, or underlying disease between the two groups. This is supported by a cohort study by Long et al. (2020), who found that initiation of oxygen treatment more than 2 days after onset of hypoxia symptoms (OR, 1.92; 95% CI, 1.20 to 3.10) was significantly associated with the risk of death, and by Menga (2021), who found no difference between individuals with early or late NIV failure. Carillo Hernandez-Rubio (2020) states this clearly: physiological and biochemical factors influence a patient's need for intubation – NIV as a therapy is not associated with reduced need for mechanical ventilation.

What signs or symptoms indicate that a COVID-19 patient requires mechanical ventilation instead of receiving HHHFO?

No direct evidence was identified that described best practices for identifying when to move a patient to mechanical ventilation from non-invasive ventilation.

Patients who were successful on HHHFO (i.e. did not require mechanical ventilation) had consistently higher PO_2/FiO_2 values at HFNC initiation (at least 100 mmHg) than those who failed HFNO (Beduneau et al., 2021; Hu et al., 2020; Vianello et al., 2020). They also had lower serum lactate dehydrogenase (LDH), higher creatinine, and lower values of PCO_2 and bicarbonate in the arterial-blood gas test before starting HFNC (Menga et al., 2021; Panadero et al., 2020).

The ROX index appears to be a useful measure for estimating the success or failure of high-flow oxygen therapy. ROX index values below 5.5 that do not increase over time (up to 16 hours) is strongly associated with increased risk of intubation (Palacios Chavarria et al., 2021; Panadero et al., 2020). Patients who did not require intubation had an increasing ROX index value above 5.5 at baseline and increasing as therapy continued is a good predictor of NIV success (sensitivity of 61.1%, a specificity of 84.6%, a positive predictive value of 68.8%, a negative predictive value of 79.8%) (Palacios Chavarria et al., 2021; Hu et al., 2021). ROX has been shown independently to be a valid predictor of intubation risk in patients with COVID-19 pneumonia (Suliman et al, 2021).

The SAPS II score also appears to be associated with NIV failure – patients with a higher median SAPS II score (39 (28 to 50) vs. 27 (22 to 31), P = 0.0031) (Beduneau et al., 2021) had a slightly higher risk of requiring intubation than those with a lower SAPS II score (adjusted hazard ratio per unit increase 1.039 [95% CI 1.018–1.061], P < .001) (Menga et al., 2021)

Non-invasive Ventilation for Acute COVID-related Hypoxemia or Respiratory Failure

No RCTs were identified that addressed the research questions for this review (stated below). The evidence from the identified guidelines is described above.

1. What is the clinical effectiveness of NIV (i.e., CPAP or Bilevel PAP), compared to HHHFO or intubation, for adult inpatients with acute COVID-related hypoxemia/respiratory failure?
2. Under what clinical conditions and in what inpatient setting is NIV more appropriate than HHHFO or intubation for managing adults with acute COVID-related hypoxemia/respiratory failure?
3. What are the risks associated with NIV for adult inpatients with acute COVID-related hypoxemia/respiratory failure compared to HHHFO or intubation?

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Table 3. Data extraction table of included studies for the research questions respecting HHHFO. Where possible, statements were copied verbatim from the reference text.

Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
Beduneau et al., 2021 France	Retrospective cohort study	All consecutive patients admitted to these two ICUs during the 28 days following the first SARS-CoV-2 pneumonia admission on March 13th, 2020. Diagnosis of SARS-CoV-2 pneumonia was based on clinical characteristics, chest imaging and real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay N= 43	HFNC success (intubation not required) HFNC was initiated at ICU admission in the majority of patients (33, 76%), with a median flow of 50 (45 to 50) L/min and a median FiO2 of 0.6 (0.5 to 0.8).	HFNC failure (intubation required)	- Twenty-nine (67%) patients were not intubated while 14 (33%) were intubated - Intubated patients more frequently had diabetes (43% vs. 10%, P = 0.04). - Patients with extensive lesions at chest CT (≥ 25%) were more frequently intubated during ICU stay (P = 0.012). - Patients with higher median SAPS II and SOFA D1 scores (respectively, 39 (28 to 50) vs. 27 (22 to 31), P = 0.0031 and 5 (2 to 8) vs. 2 (2 to 2.2), P = 0.0019), and a lower median PaO2/FiO2 (P/F) ratio (98 (63 to 109) vs. 178 (126 to 206), P = 0.0005) were more frequently intubated. Among not-intubated patients, the lowest P/F was 131 mmHg. - In patients with invasive ventilation, we observed more hemodynamic and kidney failure (respectively, 13 vs. 0, P = 0.002 and 5 vs. 2, P = 0.026), a longer median length of ICU stay (28 (19 to 28) vs. 6 (3 to 8) days, P = 0.00001) and more mortality (3 vs. 0, P = 0.013)	- HFNC could represent a safe and effective strategy of first-line oxygenation for patients with severe hypoxemic pneumonia due to SARS-COV-2 - The good outcome of our patients treated with HFNC was associated with a decreased risk of subsequent intubation. - This French clinical experience supports the use of HFNC as first line management in patients with acute respiratory failure due to SARS-COV-2 pneumonia for whom standard face mask oxygen does not provide adequate respiratory support. Note: small sample size, no risk calculations; early pandemic so there were no complementary treatments (such as steroids or proning)
Carrillo Hernandez-Rubio, 2020 Spain	Prospective cohort study	Adults with a positive PCR for SARS-CoV-2 and admitted to the Intermediate Respiratory Care Unit with tachypnea, use of accessory musculature or Sp_{O2} <92% despite Fi_{O2}> 0.5 N= 70	In patients presenting a Sp_{O2} <92% despite Fi_{O2}> 0.5 without a RR of > 30 breaths/minute or use of accessory muscles upon admission to the IRCU, treatment with HFNC (AIRVO 2, Fisher and Paykel healthcare) was started with an initial flow of 60 L/min, a temperature of 37.0°C and a Fi_{O2} between 0.5 and 1 with the objective of a Sp_{O2}> 92%	Mechanical (endotracheal) intubation	- Median age was 60 years (range: 50.7–71.2) - 77.1% were male patients. - 55.7% of patients ascertained were obese. - On admission, the median Pa_{O2}/Fi_{O2} was 83 mmHg (range: 55 to 142) and the mean SAPS II 34.3 ± 7.9 (SD). - 55.7% of the patients required HNFC and 27.1% required NIV in CPAP or BPAP mode, and frequent Helmet use (63.2%).	- Physiological and biochemical factors influence a patient's need for intubation – NIV as a therapy is not associated with reduced need for ETI - Regression modelling for predictive variables of ETI showed that proning was independently associated with the need for intubation (adjusted OR of 0.05, 95% CI 0.005 to 0.54, p = 0.001). (The variables age, sex,

Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
			In patients with RR> 30 breaths/minute, severe dyspnea or use of accessory muscles, support was started with IRCU or home ventilators (V60 Philips Respironics, Vivo 55 Breas, Vivo 60 Breas and Astral 150 Resmed) in CPAP or bilevel pressure mode		- 37.1% of patients required ETI, 58.6% of patients suffered major medical complications, and mortality was 24.3% - No significant differences were observed in the type of respiratory support received, the ventilation parameters, the type of interface or in the rest of the pharmacological treatment used between patients who required ETI and those who did not	Pa_{O2}/Fi_{O2}, lymphocytes, D-dimer, procalcitonin, IL-6, pronation, the use of acetylcysteine, azithromycin, betaferon and cyclosporin were included) - 37.1% of patients with severe respiratory failure due to COVID-19 managed with non-invasive respiratory support in the IRCU ETI was needed, observing a significantly lower complication and death rates at 28 days in patients were intubation could be avoided.
Deng et al., 2021 China	Retrospective cohort study	Elderly patients (≥65 years) with confirmed SARS-CoV-2 infection, treated with HFNC between January and March 2020 N=110	Early HFNC: HFNC treatment when 200 mmHg < PO_2/FiO_2 ≤ 300 mmHg	Late HFNC: First treated with conventional oxygen therapies (e.g., low flow nasal catheter ventilation) and then HFNC when 100 mmHg < PO_2/FiO_2 ≤ 200 mmHg	- median age of the 110 patients was 71 (IQR 68-78; range 65 to 89) years, - 65 (59.1%) were male - No significant differences on admission SpO_2, PaO_2/FiO_2, SOFA scores and APECHII scores between early and late HFNC groups - Early HFNC were less likely to have secondary infection or severe ARDS, and less likely to receive prone position ventilation and invasive mechanical ventilation than the patients who receive late HFNC. - Early HFNC had a lower likelihood of developing severe pneumonia, manifested as more than 50% increase in pneumonitis foci on chest CT scan during disease progression - Early HFNC were less likely to admit to ICU, less likely to stay in ICU longer than 7 days, had less chance to develop severe ARDS and had longer time from COVID-19 onset to severe ARDS (if any)	- 10.5% patients in the early HFNC group converted to invasive mechanic ventilation, which is in contrast to the 52.7% in the late HFNC group - Starting HFNC or invasive mechanical ventilation at a relatively late stage of disease severity such as moderate to severe ARDS may prompt the physician to apply high FiO_2 - Post-hoc subgroup analysis in the late HFNC group revealed that FiO_2 of survivors was significantly lower than that of the non-survivors and initial targeted SpO_2 was also relatively higher in the non-survivor subgroup Note: possible confounding from pharmaceutical therapies (not described in methods)

Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
Franco et al., 2020 Italy	Prospective cohort study	Patients with confirmed coronavirus disease 2019 referred to pulmonology units N= 670 (of 704 candidates)	High-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) [Only HFNC considered for this review; n=163]		- After adjustment for age, baseline P_{aO2}/F_{iO2} ratio, number of comorbidities and steroid usage, HNFC had no significant reduction in risk of 30-day mortality, ETI, or length of hospital stay compared to other NIV modes - Patients with a P_{aO2}/F_{iO2} ratio <50 presented a higher 30-day mortality rate and a higher rate of ETI (p<0.001 and p<0.001, respectively).	NRS devices is feasible in patients with ARF due to SARS-CoV-2 infection treated outside ICUs, in newly developed dedicated COVID respiratory monitoring units, formerly respiratory wards, and in respiratory intermediate care units. Note: high risk of bias from confounding; sample size decided after data collection
Hu et al., 2020 China	Retrospective cohort study	All patients initially admitted to the respiratory department instead of ICU and treated with HFNC were included between 1 January and 1 March 2020. N= 105	Success or failure of HFNC therapy (indicated for patients with SpO2≤92% and / or RR≥25 times/min under nasal tube oxygen inhalation 10L/min or mask oxygen supply)		- HFNC success patients had higher SpO_2/FiO_2, PaO_2/FiO_2 and lower RR at 6,12 and 24h of HFNC onset - The SpO_2/FiO_2, PaO_2/FiO_2 and ROX index gradually increased in the HFNC success group, and gradually declined in the HFNC failure group - ROX index greater than 5.55 at 6h after HFNC onset, as a predictor of good prognosis has a sensitivity of 61.1%, a specificity of 84.6%, a positive predictive value of 68.8%, a negative predictive value of 79.8%. - ROX index greater than 5.55 at 6h of HFNC application is the most relevant predictor of HFNC success (OR, 17.821; 95% CI, 3.741-84.903; p<0.001)	- HFNC was an effective treatment for these patients, and approximately 61.9% of patients showed improved oxygenation and were able to successfully withdraw from HFNC. - ROX index is a suitable predictor of HFNC success considering both statistical and clinical significance Note: risk of bias from confounding
Long et al., 2020 2021	Retrospective cohort study	All patients diagnosed with COVID-19 were classified as having mild, severe, or critical illness according to the Guidance for Corona Virus Disease 2019	1. Interferon-alpha (IFN-α): 5 million U or equivalent dose per time for adults, 2 ml injection of sterile water, twice daily atomization inhalation. 2. Lopinavir/ritonavir (LPV/r): 200 mg/50 mg/capsule for adults, 2 capsules per time, twice a day, for no more than 10 days.		- Of 1362 confirmed COVID cases, 206 (15.1%) died and 1156 (84.9%) were discharged from the hospital. Of the patients discharged from the hospital, 628 (54.3%) had severe illness, including 331 (28.6%) patients who developed critical illness	Initiation of oxygen treatment less than 2 days after onset after onset of hypoxia symptoms and the use of IFN-a among critically ill patients were significantly associated with lower risk of COVID-19 mortality.

Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
		N= 1362	3. Ribavirin: 500 mg/time, 2–3 times a day, for no more than 10 days. 4. Chloroquine or hydroxychloroquine (CQ or HCQ): for patients over 50 kg, 500 mg every time, twice a day, for no more than 7 days of treatment; for patients less than 50 kg, 500 mg every time for day 1–2, twice a day, 500 mg every time for day 3–7, once a day. 5. Arbidol; 200 mg, 3 times a day, for no more than 10 days. Oxygen therapy could be started at a flow rate of 5 L/min, and the target oxygen saturation was indicated by a pulse oxygen saturation ≥90% in nonpregnant adult patients, ≥92–95% in pregnant patients, and ≥94% in patients who were critically ill with severe respiratory distress, shock, or coma. If standard oxygen therapy failed, mechanical ventilation was considered; high flow nasal catheter oxygen or noninvasive ventilation (for example, bilevel positive airway pressure mode) could also be used.		- During hospitalization, 1136 (83.4%) patients received oxygen therapy beginning a median of 11 days (IQR 8–17) after symptom onset and continuing for a median of 16 days (IQR 9–23). - 244 (17.9%) patients received noninvasive mechanical ventilation treatment beginning a median of 14 days (IQR 10–18) after symptom onset and continuing for a median of 6 days (IQR 3–11) - Initiation of oxygen treatment more than 2 days after onset after onset of hypoxia symptoms (OR, 1.92; 95% CI, 1.20 to 3.10) was significantly associated with the risk of death	Note: risk of bias from confounding drug therapies
Mellado-Artigas et al., 2021 Spain	Prospective cohort study	Adult patients (≥ 18 years old) admitted to the ICU between March 12 and August 13, 2020. Patients were included if they had positive confirmatory nasopharyngeal or pulmonary tract sample and received support with either HFNO or intubation on the first day of ICU admission. N= 122 matched patients (61 per group)	HFNO as the initial oxygenation strategy in the first 24 h of ICU admission (“conservative group”)	Early invasive mechanical ventilation (within the first day of ICU admission; “early intubation group”)	- HFNO was associated with an increase in ventilator-free days (VFD) (mean difference 8.0 days; 95% CI 4.4 to 11.7 days) - HFNO associated with a reduction in ICU length of stay (mean difference -8.2 days; 95% CI -12.7 to -3.6 days) - Intubation rate was 38% in the conservative group (compared to an expected 100% in the early intubation group) - No difference was observed in all-cause in-hospital mortality between groups (OR 0.64; 95% CI 0.25 to 1.64)	HFNO was associated with an increase in VFDs and shorter ICU length of stay when compared to an early intubation strategy. No significant differences were evident in all cause in-hospital mortality.
Menga et al., 2021 Italy	Prospective cohort study	All consecutive adult patients admitted to the ICU between March 12 and April 20 due to hypoxemic respiratory failure	NIV used for COVID-19 hypoxemia	NIV for hypoxemic respiratory failure and bilateral infiltrates from other etiologies	- Fifty-two (61%) subjects required endotracheal intubation. All subjects were intubated due to the lack of improvement in oxygenation and dyspnea	- High rate of NIOS failure (61%) - In acute hypoxemic respiratory failure from other causes, NIOS failure might detrimentally affect

Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
		with confirmed RT-PCR diagnosis of COVID-19 who received noninvasive oxygenation (ie, NIV or high-flow nasal cannula) as first-line treatment for hypoxemic respiratory failure N= 104		from a previous observational study	- In the Cox regression analysis, the independent factors associated with NIOS failure were SAPS II score (adjusted hazard ratio per unit increase 1.039 [95% CI 1.018–1.061], P < .001) and serum LDH at arrival (adjusted hazard ratio per unit increase 1.002 [95% CI 1.000–1.004], P ≤ .01) - No significant difference between individuals with early vs. late NIV failure	clinical outcomes by delaying intubation and allowing self-inflicted lung injury during treatment - It is possible that nonventilatory features (eg, the microvascular involvement of the disease and the unavailability of etiologic treatments) play an important role in determining NIOS treatment outcome in COVID-19 disease Notes: early pandemic prior to evidence of steroid effectiveness as a treatment.
Palacios Chavarria et al., 2021 Mexico	Prospective cohort study	Patients aged ⩾18 years who were admitted to the temporary COVID-19 hospital with a confirmed diagnosis of COVID-19 [as verified by PCR and hypoxemic respiratory failure (PaO2 ⩽60 mmHg) N= 378	HFNO treatment success (did not require IMV)	HFNO failure (required IMV)	- HFNC success rate, defined as patients who did not require IMV, was 71.4% (n = 270; 95% CI 66.6–75.8) compared with 28.6% (n = 108; 95% CI 24.2–33.4) of patients who required IMV. - Patients with HFNC success rarely required admission to the ICU and had shorter lengths of hospital stay [19/270 (7.0%) and 15.0 days, respectively] than those who required IMV [104/108 (96.3%) and 26.5 days, respectively - In patients with HFNC success, Rox index values increased from 5.98 at baseline to 6.41, 6.83, 7.02, 7.37, 7.87, and 8.20 after 1, 2, 4, 6, 12, and 16 hours, respectively. - In patients with HFNC failure, Rox index values remained low from 5.40 at baseline to 5.70, 5.88, 5.76, 5.93, 5.74, and 5.62 after 1, 2, 4, 6, 12, and 16 hours, respectively	CALL score at admission predicted a linear increase in the risk of IMV, with an HR of 1.27 for every point increase. The Rox index at 1 hour after starting HFNC predicted an 18% decrease in the risk of IMV for every point increase; in contrast, steroid treatment predicted a 66% decrease in the risk of IMV compared with the absence of steroid treatment.

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Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
					- In patients with HFNC success, the median (IQR) ratio of SpO2 over FiO2 (SPFI) increased from 135.7 (115.3, 160.0) after 2 hours to 158.4 (127.2, 192.2) after 16 hours of HFNC. - In patients with HFNC failure, the median (IQR) SPFI ratio decreased from 115.0 (98.0, 140.0) after 2 hours to 110.4 (96.5, 134.9) after 16 hours of HFNC. - CALL score at admission (adjusted HR 1.27; 95% CI 1.09–1.47; $p < 0.01$), Rox index at 1 hour (adjusted HR 0.82; 95% CI 0.70–0.96; $p = 0.02$), and absence of treatment with steroids (adjusted HR 0.34; 95% CI 0.19–0.62; $p < 0.0001$) were all significant predictors of HFNC failure	
Panadero et al., 2020 Spain	Retrospective cohort study	Patients included in the analysis were between the ages of 18 and 80, who had PaO_2/FiO_2 <200mmHg or SpO_2/FiO_2 ratio <240, and who were treated with high-flow oxygen therapy through nasal cannula N= 40	Successful HFNO treatment	Failed HFNO treatment	- Mean age was 58.9 years, and 70% were men (21 experienced therapy failure) - Overall mortality rate was nine patients (22.5%), all of whom were in the failed HFNC therapy group - The patients who did not require intubation had lower serum LDH levels and higher creatinine levels. They also presented lower values of PCO_2 and bicarbonate in the arterial-blood gas test before starting HFNC - SpO_2/FiO_2 ratio after starting HFNC was significantly higher in the group that did not require intubation (113.4±6.6 *vs* 93.7±6.7; p=0.020), as was the ROX index (5.0±1.6 *vs* 4.0±1.0; p=0.018) - ROX value of less than 4.94 at 2-6 hrs post-initiation was associated with increased risk of intubation (HR 4.03 [95% CI 1.18 – 13.7]; p=0.026)	- HFNC enabled us to treat ARDS successfully in a high proportion of patients (47.5%) without requiring invasive ventilatory support and with low mortality - Patients with a ROX <4.94 after HFNO initiation may benefit from closer monitoring or early intubation

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Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
Patel et al., 2020 United States	Retrospective cohort study	Patients tested positive for COVID-19 using nasopharyngeal RT-PCR or patients with high clinical suspicion and findings suggestive of COVID-19 based on high-resolution CT of the chest, with moderate-to-severe hypoxaemic respiratory failure and were on oxygen delivery via HFNT N= 104	Successful HFNO treatment ("non-intubation group")	Failed HFNO treatment ("intubation group")	- The average age was 60.66 (±13.50) years, 49 (47.12 %) were female, 53 (50.96%) were African-American, 23 (22.12%) Hispanic. - mortality was 14.44% (n=15) in our cohort with 13 (34.4%) in the intubation group and 2 (2.9%) in the non-intubation group (p=0.0018) - SF ratios were significantly different between the two groups at baseline, with the intubation group having much lower SF ratios compared with those who remained on HFNT (111.03±34.09 vs 127.9+43.47, p=004) - ICU LOS was higher for the intubation group (10.45 days±6.12 vs 4.05 ± 2.64 days, p=0.0008)	- Of 104 patients (23.3%) treated initially with HFNT, 64.4% remained on HFNT and were able to avoid escalation to non-invasive and IMV. - Survival advantage cannot be attributed to HFNT based on the study's retrospective design, use of HFNT did not result in worsened outcomes either.
Teng et al., 2020 China	RCT	Adults >18 years; the patients met the diagnostic criteria for patients with severe COVID-19 in the COVID-19 Diagnosis and Treatment Plan N=22 (12 HFNC, 10 conventional oxygen treatment)	HFNC oxygen therapy. Initial parameters: temperature was 37°C, flow rate was 50 L/min, and oxygen concentration was 50%. Parameters were adjusted according to blood oxygen saturation level (SpO_2), blood gas and tolerance, maintaining SpO_2 above 93%.	Conventional oxygen therapy (COT); oxygen utilizing a nasal catheter or a common mask. Initial oxygen absorption flow set at 5 L/min, adjusted according to the condition of SPO_2, maintaining SpO_2 above 93%	- Age, gender, interval from onset to diagnosis and underlying diseases between the two groups were not significantly different - Differences in HR, RR and PaO_2/FiO_2 at 0 hours of treatment between the two groups were not significant - At 6 hours after treatment with the two oxygen therapies, HR, RR and PaO_2/FiO_2 were better in the HFNC oxygen therapy group than in the COT group ($P < .05$) - At 24 and 72 hours after treatment, PaO_2/FiO_2 was better in the HFNC oxygen therapy group than in the COT group ($P < .05$) - At 6, 24 and 72 hours after treatment, RR was lower in the HFNC oxygen therapy group than in the COT group, and PaO_2/FiO_2 was higher in the HFNC	Compared with COT, early application of HFNC oxygen therapy in patients with severe COVID-19 can improve oxygenation and RR, and HFNC oxygen therapy can improve the infection indexes of patients and reduce the length of stay in the ICU of patients.

Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
					oxygen therapy group than in the COT group - The length of ICU stay was 4.00 ± 0.74 days in the HFNC oxygen therapy group and 4.90 ± 1.00 days in the COT group, and the difference was statistically significant (*P* = .024) - Length of hospitalization was not significantly different	
Vianello et al, 2020 Italy	Retrospective cohort study	(1) laboratory-confirmed COVID-19 infection; (2) PaO2/FIO2 ratio <300 mm Hg, FIO2 being determined as previously described; (3) failure of conventional O2-therapy delivered through a non-rebreathing mask with a reservoir bag to maintain SaO2 ≥92%. N= 28 (consecutively admitted)	Success: patients who had a successful outcome from HFNO therapy, as defined by reversal of hypoxemia (SaO2 ≥92%), no need for NIV and/or invasive mechanical ventilation (IMV), discharge from RICU, with the patient alive and conscious for at least 48 hours after discharge.	Failure group: patients who had an unsuccessful outcome, defined as the need for NIV or IMV by ETI and/or death while on HFNC support	- Male:female ratio was 3 to 1 (21 vs 7). The patients were classified, in accordance with the WHO criteria, as showing moderate (17 cases) or severe (11 cases) acute respiratory distress at admission - Nineteen (67.8%) succeeded HFNC as hypoxemia was reversed and they were discharged from the RICU and were still alive on day 15 after discharge. Nine patients (32.2%) failed HFNC and received NIV (five required IMV) - All nine failing patients had lower PaO2/FIO2 (76 (53–190) vs 126 (52–296) mm Hg; p=0.0194) and higher serum C reactive protein level (130 (110–270) vs 110 (29–180); p=0.01277) than HFNO success group - Patients with PaO2/FIO2 at admission ≤100 mm Hg showed a greater rate of treatment failure (7/9 (77.8%)), as opposed to those with PaO2/FIO2 >100 mm Hg (6/21 (31.6%); p=0.0246), with an OR of failure of 7.6 (95% CI 1.2 to 48.1)	- PaO2/FIO2 at admission had prognostic relevance - patients with PaO2/FIO2 values ≤100 mm Hg had an increased risk of treatment failure.
Wendel Garcia et al., 2021 International	Prospective cohort study	Patients were included in the present substudy if they required standard oxygen therapy (SOT) (≥10 L/min), HFNC, NIV, or IMV at the	(1) SOT group: patients receiving SOT with an oxygen flow of ≥10 L/min (FiO2 was approximated based on the delivered oxygen flow)		-After matching, 351 patients (85 SOT, 87 HFNC, 87 NIV and 92 IMV) were included in the final analysis - ICU mortality rate was higher (p = 0.016) in patients initially ventilated with NIV	- Compared to the other respiratory support strategies, NIV was associated with higher ICU mortality rates.

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Reference	Study Type	Population	Intervention or Exposure	Comparator	Outcomes	Conclusions
		time point of admission to the ICU defined as day 0. N=351	(2) HFNC group: patients receiving HFNC, defined as a device delivering humidified and heated oxygen at a flow rate above 30 L/min (3) NIV group: patients receiving NIV, irrespective of interface, mode and ventilator type employed (4) IMV group: intubated patients receiving IMV		than in the other groups (SOT: 18%, HFNC: 20%, NIV: 37%, IMV: 25%) - median duration of the in-hospital stay until intubation was longer ($p<0.001$) in the NIV group (4 [IQR, 3–7] days) compared to the other three groups (SOT: 3 [1–5] days, HFNC: 3 [2–6] days, IMV: 1 [0–3] days) - Patients who were initially treated with HFNC and NIV, and later required IMV, had longer ($p = 0.018$) ICU lengths of stay than patients under initial SOT when compared to early IMV - NIV was independently associated with a higher overall ICU mortality (adjusted HR 2.67, 95% CI [1.14–6.25]) as well as with an increased ICU mortality rate (adjusted HR 2.96, 95% CI [1.07–8.23]) and a prolonged length of ICU stay (adjusted HR 0.57, 95% CI [0.33–0.97]) in patients failing NIV and requiring delayed IMV, as opposed to the other respiratory support strategies	- The excess mortality observed in patients treated with NIV in this study might thus be explained by the longer period of harmful spontaneous breathing in patients failing NIV therapy, exacerbated by an increased respiratory rate and disproportionate tidal volumes induced by NIV therapy

Table 4. Grey literature evidence extraction table of included studies for the research questions regarding NIV. Where possible, statements were copied directly from the reference text.

Reference	Jurisdiction	Year	Guidance
Chalmers et al., 2021 European Respiratory Society	Europe	2021	- We suggest high flow nasal cannula oxygen (HFNC) or non-invasive continuous positive airway pressure (CPAP) delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxaemic acute respiratory failure in the absence of immediate indications for invasive mechanical ventilation (conditional recommendation, very low quality of evidence) - Notes accompanying this recommendation: HFNC and non-invasive CPAP are classified as aerosol generating and should therefore be delivered in a safe environment with staff wearing appropriate personal protecting equipment - HFNC and non-invasive CPAP should not delay mechanical ventilation in patients who are not responding to treatment - Prone positioning may improve oxygenation in non-intubated patient with acute hypoxaemic respiratory failure and is widely used for mechanically ventilated patients with COVID-19.
National COVID-19 Clinical Evidence Taskforce, 2021	Australia	2021	- [Consensus Recommendation]: Guiding principles of care: For patients with COVID-19 for whom respiratory support (HFNO/NIV) is being considered, decisions should balance likelihood of patient benefit against the risk of infection for healthcare workers. For patients with COVID-19 receiving respiratory support (HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place. Closed circuit NIV should be used. - [Conditional recommendation]: Consider using HFNO therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If HFNO is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only. Use the lowest flow necessary to maintain oxygen saturation ≥ 92%. - [Conditional recommendation]: Consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If NIV is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only. - [Consensus recommendation]: Do not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies. - [Conditional recommendation]: For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning for at least 3 hours per day as tolerated. When positioning a patient in prone, ensure it is used with caution and accompanied by close monitoring of the patient. Use of prone positioning should not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised less invasive respiratory therapies.
Messer et al., 2021 British Thoracic Society and Intensive Care Society	UK	2021	- The trigger for consideration for escalation of patients on general wards to an RSU should be the inability to maintain oxygen saturations ≥94% on an inspired oxygen <40% - Signs of CPAP/HFNO/NIV failure include: limited initial response within 6h, lack of improvement within 3 days, unchanged/increasing work of breathing, not tolerating CPAP/NIV breaks - CPAP and NIV impact on suitability for ECMO support so it is important to consider critical care early when appropriate

Reference	Jurisdiction	Year	Guidance
			- Aim for target saturations as per NICE guideline for oxygen use during COVID-19 (92-96% or 88-92% in those at risk of hypercapnic respiratory failure)
World Health Organization, 2021	International	2021	*Severe Pneumonia from COVID-19* - We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target SpO2 ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target SpO2 > 90% or ≥ 92–95% in pregnant women. Deliver oxygen flow rates using appropriate delivery devices (e.g. use nasal cannula for rates up to 5 L/min; Venturi mask for flow rates 6–10 L/min; and face mask with reservoir bag for flow rates 10–15 L/min). - Patients hospitalized with COVID-19 require regular monitoring of vital signs (including pulse oximetry) and, where possible, utilization of medical early warning scores (e.g. NEWS2, PEWS) that facilitate early recognition and escalation of treatment of the deteriorating patient - **Conditional recommendation:** We suggest awake prone positioning of severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes high-flow nasal oxygen) or non-invasive ventilation (conditional, low certainty evidence). - Applying the agreed values and preferences, the GDG inferred that almost all well-informed patients would want to undergo prone positioning if awake, requiring oxygen or non-invasive respiratory support, given the lack of harm from the observational studies and panel experience *ARDS from COVID-19* - Patients with hypoxaemic respiratory failure and haemodynamic instability, multiorgan failure or abnormal mental status should not receive HFNO or NIV in place of other options such as invasive ventilation - We recommend prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support
National Institutes of Health, 2021	United States	2021	*Nonmechanically Ventilated Adults with Hypoxemic Respiratory Failure* - 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). In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available (BIIa). - For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation (CIIa). - The Panel recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (AIII). - The optimal oxygen saturation (SpO2) in adults with COVID-19 is uncertain. However, a target SpO2 of 92% to 96% seems logical considering that indirect evidence from experience in patients without COVID-19 suggests that an SpO2 <92% or >96% may be harmful.

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Reference	Jurisdiction	Year	Guidance
National Institute for Health and Care Excellence, 2021	England	2021	- [Conditional recommendation] Consider offering continuous positive airway pressure (CPAP) to people with COVID-19 when: 1) They have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, and 2) escalation to invasive mechanical ventilation would be an option but it is not immediately needed, or 3) it is agreed that respiratory support should not be escalated beyond CPAP. - [Conditional recommendation against] Do not routinely offer high-flow nasal oxygen as the main form of respiratory support for people with COVID-19 and respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate. - For people with COVID-19 having continuous positive airway pressure, ensure: 1) there is access to critical care providers for advice, review and prompt escalation of treatment if needed (such as when treatment has failed) 2) regular review by an appropriate senior clinician (such as every 12 hours) and more frequent review if needed, in line with the British Thoracic Society guidance on respiratory support units and the Faculty of Intensive Care Medicine guidelines on the provision of intensive care services, and 3) regular assessment and management of symptoms alongside non-invasive respiratory support.

Limitations

This review was limited by several factors that must be considered when assessing the findings. First, this is a rapid review. The search was thorough, but not systematic. In addition, the search was limited to literature published in English in the past 2 years. For these reasons, it is possible that relevant studies were not captured in the database search.

As with most reviews of COVID-19-related evidence, this review is limited by the lack of controlled trial evidence. Observational studies cannot show causation, only association; thus, it is difficult to determine if the intervention being studied truly has clinical benefit or if benefit is due to the characteristics of the patient. These studies also suffer from the rapid pace of COVID-19 research, where studies are haphazardly designed with little attention paid to limiting bias. As a result, the studies included in this review are at high risk of bias from confounding.

With respect to the body of evidence, the terminology around high-flow oxygen is not standardized, which makes searching for grey literature challenging. The most common terms include “high flow nasal cannula”, “high flow nasal oxygen”, “heated humidified high-flow nasal cannula”, “heated humidified high-flow oxygen”, and “high-flow oxygen”. It is therefore difficult to determine if each term refers to the same systems and mode of therapy.

Conclusions

Based on the evidence presented in the synthesis above, the following conclusions can be made:

- The body of evidence on this topic is estimated to be of low quality. It is largely cohort studies at high risk of confounding, and guidance based on this review should acknowledge this limitation.
- No peer-reviewed RCTs were identified to address the research questions specifically relating to CPAP and Bilevel PAP as therapy for COVID-19.
- Guidelines from the WHO, Europe, UK, USA, and Australia unanimously recommend using non-invasive therapies (such as HHHFO, CPAP, or Bilevel PAP) in hypoxemic patients requiring oxygen supplementation beyond what conventional oxygen therapy can provide, but for whom invasive mechanical ventilation is not yet indicated.
- The principal risk to patients arising from non-invasive oxygen supplementation in COVID-19 appears to be delayed intubation, which can be mitigated by close monitoring and not trying to rescue respiratory function with additional non-invasive therapy or positioning once therapy failure has been determined.
- One RCT found that early oxygen therapy via high-flow nasal cannula (HHHFO) resulted in significantly better respiratory rate (RR), heart rate (HR) and PaO_2/FiO_2 at 6 hours post treatment initiation compared to conventional oxygen therapy. Observational studies support this finding and show that HHHFO can reduce the ICU length of stay and ventilator-free days, but is not necessarily associated with a decrease in mortality.
- Benefit from non-invasive ventilation or HHHFO therapies is associated with early intervention, rather than with patient characteristics. The need for intubation is influenced by the patient’s physiological and biochemical characteristics. NIV as a therapy is not clearly associated with reduced need for mechanical ventilation.
- No direct evidence was identified that described best practices for identifying when to move a patient to mechanical ventilation from non-invasive ventilation. The ROX index score is a valid prognostic measure of HHHFO success or failure. ROX index values below 5.5 that do not increase over time (up to 16 hours after start of HHHFO therapy, or limited response within the first 6 hours) is strongly associated with increased risk of intubation, while patients who did not require intubation had a ROX index value above 5.5 at baseline that increased as therapy continued.

References

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Appendix

List of Abbreviations

AHS: Alberta Health Services

CI: Confidence Interval

COVID-19: Coronavirus Disease 2019

CPAP: Continuous Positive Airway Pressure

HFNC: High Flow Nasal Cannula

HFNO: High Flow Nasal Oxygen

HHHFO: Heated Humidified High-Flow Oxygen

HR: Heart Rate

ICU: Intensive Care Unit

KRS: Knowledge Resource Services

LDH: lactate dehydrogenase

MSCN: Medicine Strategic Clinical Network

NICE: National Institute for Health and Care Excellence

NIV: Non-invasive Ventilation

OR: odds ratio

PAP: Positive Airway Pressure

PPE: Personal Protective Equipment

RCT: Randomized Controlled Trial

RR: Respiratory Rate

UK: United Kingdom

US: United States

WHO: World Health Organization

Included Studies

Beduneau, G., Boyer, D., Guitard, P. G., Gouin, P., Carpentier, D., Grangé, S., ... & Tamion, F. (2021). Covid-19 severe hypoxemic pneumonia: a clinical experience using high-flow nasal oxygen therapy as first-line management. Respiratory Medicine and Research, 100834. https://www.sciencedirect.com/science/article/pii/S2590041221000234

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HHHFO Search

Reference	Reason for Exclusion
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Afriyie-Mensah J, Aboagye ET, Ganu VJ, Bondzi S, Tetteh D, Kwarteng E, et al. **Clinical and therapeutic outcomes of COVID-19 intensive care units (ICU) patients: a retrospective study in Ghana**. The Pan African medical journal. 2021;38:107.	Not HHHFO, not RCT

Alharthy A, Faqihi F, Noor A, Soliman I, Brindley PG, Karakitsos D, et al. **Helmet Continuous Positive Airway Pressure in the Treatment of COVID-19 Patients with Acute Respiratory Failure could be an Effective Strategy: A Feasibility Study**. Journal of epidemiology and global health. 2020;10(3):201-3.	Not RCT
Anai M, Akaike K, Iwagoe H, Akasaka T, Higuchi T, Miyazaki A, et al. **Decrease in hemoglobin level predicts increased risk for severe respiratory failure in COVID-19 patients with pneumonia**. Respiratory investigation. 2021;59(2):187-93	No NIV considered
Ashish A, Unsworth A, Martindale J, Sundar R, Kavuri K, Sedda L, et al. **CPAP management of COVID-19 respiratory failure: a first quantitative analysis from an inpatient service evaluation**. BMJ open respiratory research. 2020;7(1	Not RCT
Audley GG, Frankenfeld P, Dlamini S, Raubenheimer P, Hoare J, Cairncross L, et al. **Prolonged treatment of COVID-19 pneumonia with high-flow nasal oxygen: A story of oxygen and resilience**. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2020;110(12):1168-71.	Case report
Avdeev SN, Yaroshetskiy AI, Tsareva NA, Merzhoeva ZM, Trushenko NV, Nekludova GV, et al. **Noninvasive ventilation for acute hypoxemic respiratory failure in patients with COVID-19**. The American journal of emergency medicine. 2021;39:154-7.	Not RCT
Babar I, Ekenna O, Clarkson MR, Boudreaux D, Bennett W, Roth R. **COVID-19 in a Mississippi Community Hospital**. Southern medical journal. 2021;114(5):305-10.	Not a study of NIV effectiveness
Barrasa H, Rello J, Tejada S, Martin A, Balziskueta G, Vinuesa C, et al. **SARS-CoV-2 in Spanish Intensive Care Units: Early experience with 15-day survival in Vitoria**. Anaesthesia, critical care & pain medicine. 2020;39(5):553-61	NIV not indicated
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Borgen I, Romney MC, Redwood N, Delgado B, Alea P, George BH, et al. **From Hospital to Home: An Intensive Transitional Care Management Intervention for Patients with COVID-19**. Population Health Management. 2021;24(1):27-34.	Wrong setting (ambulatory to home)
Cherian SV, Li C, Roche B, Reyes SA, Karanth S, Lal AP, et al. **Predictive factors for success of awake proning in hypoxemic respiratory failure secondary to COVID-19: A retrospective cohort study**. Respiratory medicine. 2021;181:106379	Proning (NIV incidental)
Chew SY, Lee YS, Ghimiray D, Tan CK, Chua GS. **Characteristics and Outcomes of COVID-19 Patients with Respiratory Failure Admitted to a "Pandemic Ready" Intensive Care Unit - Lessons from Singapore**. Annals of the Academy of Medicine, Singapore. 2020;49(7):434-48.	Case series; non-interventional
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Daher A, Balfanz P, Aetou M, Hartmann B, Muller-Wieland D, Muller T, et al. **Clinical course of COVID-19 patients needing supplemental oxygen outside the intensive care unit**. Scientific reports. 2021;11(1):2256	Supplemental O2, not NIV or HHHFO

Dang J-Z, Zhu G-Y, Yang Y-J, Zheng F. **Clinical characteristics of coronavirus disease 2019 in patients aged 80 years and older**. Journal of integrative medicine. 2020;18(5):395-400	Non-interventional
Dayya D, O'Neill OJ, Feiertag TD, Tuazon-Boer R, Sullivan J, Perez L, et al. **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. 2021;179:106312	Non-randomized, oxygen hood after NIV or HHHFO
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Diaz De Teran T, Gonzales Martinez M, Banfi P, Garuti G, Ferraioli G, Russo G, et al. **Management of patients with severe acute respiratory failure due to SARS-CoV-2 pneumonia with noninvasive ventilatory support outside Intensive Care Unit**. Minerva medica. 2021;112(3):329-37.	NIV not defined or controlled, not RCT
Elharrar X, Trigui Y, Dols A-M, Touchon F, Martinez S, Prud'homme E, et al. **Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure**. JAMA. 2020;323(22):2336-8.	Does not describe ventilation method
Gershengorn HB, Hu Y, Chen J-T, Hsieh SJ, Dong J, Gong MN, et al. **The Impact of High-Flow Nasal Cannula Use on Patient Mortality and the Availability of Mechanical Ventilators in COVID-19**. Annals of the American Thoracic Society. 2021;18(4):623-31.	Modelling study
Gerson-Cwilich R, Shveid-Gerson D, Noguez-Ramos A, Lopez-Zepeda L, Rodriguez-Soto BE, Villegas-Osorno DA, et al. **Biomarkers associated with coronavirus disease-19 disease progression in a Mexican hospital**. Revista Medica del Hospital General de Mexico. 2021;84(2):64-70	Non-interventional
Gresser E, Rueckel J, Puhr-Westerheide D, Schwarze V, Fink N, Kunz WG, et al. **Prognostic value of admission chest ct findings for invasive ventilation therapy in covid-19 pneumonia**. Diagnostics. 2020;10(12):1108	Non-interventional, not NIV
Haimovich AD, Ravindra NG, Stoytchev S, Young HP, Wilson FP, van Dijk D, et al. **Development and Validation of the Quick COVID-19 Severity Index: A Prognostic Tool for Early Clinical Decompensation**. Annals of emergency medicine. 2020;76(4):442-53.	Predicts mortality not NIV benefit
Hallifax RJ, Porter BM, Elder PJ, Evans SB, Turnbull CD, Hynes G, et al. **Successful awake proning is associated with improved clinical outcomes in patients with COVID-19: single-centre high-dependency unit experience**. BMJ open respiratory research. 2020;7(1).	No analysis of NIV modes separately; no non-proning control group
Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, et al. **Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19**. The Journal of allergy and clinical immunology. 2020;146(1):128-36.e4.	Non-interventional
Huespe IA, Marco A, Prado E, Bisso IC, Coria P, Gemelli N, et al. **Changes in the management and clinical outcomes of critically ill patients without COVID-19 during the pandemic**. Modificacoes no manejo e desfechos clinicos de pacientes criticos sem COVID-19 durante a pandemia. 2021;33(1):68-74	No outcomes from HHHFO or NIV described
Karamouzos V, Fligou F, Gogos C, Velissaris D. **High flow nasal cannula oxygen therapy in adults with COVID-19 respiratory failure. A case report**. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace. 2020;90(2)	Single case report
Kayem G, Lecarpentier E, Deruelle P, Bretelle F, Azria E, Blanc J, et al. **A snapshot of the Covid-19 pandemic among pregnant women in France**. Journal of gynecology obstetrics and human reproduction. 2020;49(7):101826	No ventilation outcomes

Keddie S, Ziff O, Chou MKL, Taylor RL, Heslegrave A, Garr E, et al. **Laboratory biomarkers associated with COVID-19 severity and management**. Clinical immunology (Orlando, Fla). 2020;221:108614.	No ventilation outcomes
Kodama T, Obinata H, Mori H, Murakami W, Suyama Y, Sasaki H, et al. **Prediction of an increase in oxygen requirement of SARS-CoV-2 pneumonia using three different scoring systems**. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy. 2021;27(2):336-41.	O2 requirement, not ventilation. No outcomes for ventilation
Lagi F, Piccica M, Graziani L, Vellere I, Botta A, Tilli M, et al. **Early experience of an infectious and tropical diseases unit during the coronavirus disease (COVID-19) pandemic, Florence, Italy, February to March 2020**. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2020;25(17).	No NIV, no outcomes
Lee JY, Kim HA, Huh K, Hyun M, Rhee JY, Jang S, et al. **Risk Factors for Mortality and Respiratory Support in Elderly Patients Hospitalized with COVID-19 in Korea**. Journal of Korean medical science. 2020;35(23):e223.	No outcomes from HHHFO
Liu L, Xie J, Wu W, Chen H, Li S, He H, et al. **A simple nomogram for predicting failure of non-invasive respiratory strategies in adults with COVID-19: a retrospective multicentre study**. The Lancet Digital health. 2021;3(3):e166-e74	No ventilation outcomes
Long B, Liang SY, Hicks C, Gottlieb M. **Just the Facts: What are the roles of oxygen escalation and noninvasive ventilation in COVID-19?** CJEM. 2020;22(5):587-90.	Case report + narrative review
Lopez-Castaneda S, Garcia-Larragoiti N, Cano-Mendez A, Blancas-Ayala K, Damian-Vazquez G, Perez-Medina AI, et al. **Inflammatory and Prothrombotic Biomarkers Associated With the Severity of COVID-19 Infection**. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2021;27:1076029621999099.	No outcomes from ventilation type
Lu X, Xu S. **Therapeutic effect of high-flow nasal cannula on severe COVID-19 patients in a makeshift intensive-care unit: A case report**. Medicine. 2020;99(21):e20393.	Small case series (n=4)
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Martins A, Mouro M, Caldas J, Silva-Pinto A, Santos AS, Xerinda S, et al. **Clinical characteristics and outcomes of critically ill COVID-19 patients admitted to an Infectious Diseases Intensive Care Unit in Portugal**. Critical Care & Shock. 2021;24(1):32-40	No ventilation outcomes reported
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Ni Y-N, Wang T, Liang B-M, Liang Z-A. **The independent factors associated with oxygen therapy in COVID-19 patients under 65 years old**. PloS one. 2021;16(1):e0245690	No outcomes from ventilation
Pan W, Li J, Ou Y, Wu Y, Cai S, Zhang Y, et al. **Clinical outcome of standardized oxygen therapy nursing strategy in COVID-19**. Annals of palliative medicine. 2020;9(4):2171-7	Analysis not specific to HHHFO or NIV – strategy includes upgrading and downgrading

Pande D, Kochhar A, Saini S, Ganapathy U, Gogia A. **An update on initial epidemiological profile, clinical course, and outcome of COVID-19 patients at a tertiary care center in India**. Indian Journal of Palliative Care. 2020;26:36-9	No outcomes from ventilation
Pandya A, Kaur NA, Sacher D, O'Corragain O, Salerno D, Desai P, et al. **Ventilatory Mechanics in Early vs Late Intubation in a Cohort of Coronavirus Disease 2019 Patients With ARDS: A Single Center's Experience**. Chest. 2021;159(2):653-6.	Intubation only
Piva S, Filippini M, Turla F, Cattaneo S, Margola A, De Fulviis S, et al. **Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy**. Journal of critical care. 2020;58:29-33	No outcomes from ventilation
Piwowarczyk P, Szczukocka M, Kutnik P, Borys M, Miklaszewska A, Kiciak S, et al. **Risk factors and outcomes for acute respiratory failure in coronavirus disease 2019: An observational cohort study**. Advances in clinical and experimental medicine : official organ Wroclaw Medical University. 2021;30(2):165-71	No outcomes from ventilation
Popadic V, Klasnja S, Milic N, Rajovic N, Aleksic A, Milenkovic M, et al. **Predictors of Mortality in Critically Ill COVID-19 Patients Demanding High Oxygen Flow: A Thin Line between Inflammation, Cytokine Storm, and Coagulopathy**	No outcomes due to ventilation
Procopio G, Cancelliere A, Trecarichi EM, Mazzitelli M, Arrighi E, Perri G, et al. **Oxygen therapy via high flow nasal cannula in severe respiratory failure caused by Sars-Cov-2 infection: a real-life observational study**. Therapeutic advances in respiratory disease. 2020;14:1753466620963016.	Case series, n=5
Qin C, Zhou L, Hu Z, Yang S, Zhang S, Chen M, et al. **Clinical Characteristics and Outcomes of COVID-19 Patients With a History of Stroke in Wuhan, China**. Stroke. 2020;51(7):2219-23	No outcomes from ventilation
Ramos Hernandez C, Botana Rial M, Pazos Area LA, Nunez Fernandez M, Perez Fernandez S, Rubianes Gonzalez M, et al. **Lung Ultrasound to Predict Unfavorable Progress in Patients Hospitalized for COVID-19**. Prediccion de evolucion desfavorable en pacientes hospitalizados por COVID-19 mediante ecografia pulmonar. 2021;57 Suppl 1:47-54	Spanish
Reindorf M, Newman J, Ingle T. **Successful use of CPAP in a pregnant patient with COVID-19 pneumonia**. BMJ case reports. 2021;14(3)	Case report
Retucci M, Aliberti S, Ceruti C, Santambrogio M, Tammaro S, Cuccarini F, et al. **Prone and Lateral Positioning in Spontaneously Breathing Patients With COVID-19 Pneumonia Undergoing Noninvasive Helmet CPAP Treatment**. Chest. 2020;158(6):2431-5.	Case report
Riveiro-Barciela M, Labrador-Horrillo M, Camps-Relats L, Gonzalez-Sans D, Ventura-Cots M, Terrones-Peinador M, et al. **Simple predictive models identify patients with COVID-19 pneumonia and poor prognosis**. PloS one. 2020;15(12):e0244627.	No outcomes from ventilation
Roth GA, Emmons-Bell S, Alger HM, Bradley SM, Das SR, de Lemos JA, et al. **Trends in Patient Characteristics and COVID-19 In-Hospital Mortality in the United States During the COVID-19 Pandemic**. JAMA Network Open. 2021;4(5):e218828-e	No outcomes from ventilation
Santus P, Radovanovic D, Saderi L, Marino P, Cogliati C, De Filippis G, et al. **Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: a prospective observational multicentre study**. BMJ open. 2020;10(10):e043651	Not comparative, no outcomes from ventilation
Senter R, Capone F, Cerruti L, Molinari L, Previato L, Toffolon A, et al. **Lung ultrasound patterns and clinical-laboratory correlates during covid-19 pneumonia: A retrospective study from North East Italy**. Journal of Clinical Medicine. 2021;10(6):1-12	No ventilation outcomes
Simioli F, Annunziata A, Langella G, Polistina GE, Martino M, Fiorentino G. **Clinical outcomes of high-flow nasal cannula in COVID-19 associated postextubation**	Small case series (n=9)

ECC Approved: February 11, 2022

respiratory failure. A single-centre case series. Anaesthesiology intensive therapy. 2020;52(5):373-6.	
Son M, Seo J, Yang S. **Association Between Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19 Infection in South Korea**. Hypertension (Dallas, Tex : 1979). 2020;76(3):742-9	No outcomes from ventilation
Sonsoz MR, Oncul A, Cevik E, Orta H, Yilmaz M, Ayduk Govdeli E, et al. **Wide QRS Complex and Lateral ST-T Segment Abnormality Are Associated With Worse Clinical Outcomes in COVID-19 Patients**. The American journal of the medical sciences. 2021;361(5):591-7.	No outcomes from ventilation
Suh HJ, Lee E, Park SW. **Clinical Characteristics of COVID-19: Risk Factors for Early Oxygen Requirement after Hospitalization**. Journal of Korean medical science. 2021;36(19):e139	No outcomes from ventilation
Suliman LA, Abdelgawad TT, Farrag NS, Abdelwahab HW. **Validity of ROX index in prediction of risk of intubation in patients with COVID-19 pneumonia**. Advances in respiratory medicine. 2021;89(1):1-7.	Exclude, no outcomes
Verma R, Kumar A, Nishad RK, Patawa R. **Clinical characteristics and outcome of critically ill SARS-CoV-2 patients admitted to intensive care unit of a tertiary care hospital in north india: A retrospective study**. Journal of Clinical and Diagnostic Research. 2021;15(5):UC05-UC8	No outcomes from ventilation
Virot E, Mathien C, Pointurier V, Poidevin A, Labro G, Pinto L, et al. **Characterization of pulmonary impairment associated with COVID-19 in patients requiring mechanical ventilation**. Caracterizacao do comprometimento pulmonar associado a COVID-19 em pacientes com necessidade de ventilacao mecanica. 2021;33(1):75-81.	No outcomes from ventilation
Wu X, Li C, Chen S, Zhang X, Wang F, Shi T, et al. **Association of body mass index with severity and mortality of COVID-19 pneumonia: a two-center, retrospective cohort study from Wuhan, China**. Aging. 2021;13(6):7767-80	No outcomes from ventilation
Xiao L, Shanxiang X, Lu X, Xu S. **Therapeutic effect of high-flow nasal cannula on severe COVID-19 patients in a makeshift intensive-care unit: A case report**. Medicine. 2020;99(21):1-4	Small case series (n=4)
Xu Q, Wang T, Qin X, Jie Y, Zha L, Lu W. **Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19: a case series**. BioMed Central; 2020. p. 1-3.	No comparator, outcomes not of interest
Yang SS, Lipes J, Dial S, Schwartz B, Laporta D, Wong E, et al. **Outcomes and clinical practice in patients with COVID-19 admitted to the intensive care unit in Montreal, Canada: a descriptive analysis**. CMAJ open. 2020;8(4):E788-E95	No comparative outcomes
Yang X, Yu Y, Xu J, Shu H, Xia Ja, Liu H, et al. **Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study**. The Lancet Respiratory medicine. 2020;8(5):475-81.	No outcomes from ventilation
Zacharioudakis I, Aguero-Rosenfeld ME, Prasad P, Zervou F, Basu A, Weisenberg S, et al. **Association of SARS-CoV-2 genomic load in nasopharyngeal samples with adverse COVID-19 patient outcomes: A retrospective analysis from an academic hospital center in New York City**. Open Forum Infectious Diseases. 2020;7(SUPPL 1):S274-S5	Conference abstract
Zdravkovic M, Popadic V, Klasnja S, Pavlovic V, Aleksic A, Milenkovic M, et al. **Development and Validation of a Multivariable Predictive Model for Mortality of COVID-19 Patients Demanding High Oxygen Flow at Admission to ICU: AIDA Score**. Oxidative medicine and cellular longevity. 2021;2021:6654388	No outcomes from ventilation; not validated for ventilation outcomes

Zhan Z, Yang X, Du H, Zhang C, Song Y, Ran X, et al. **Early Improvement of Acute Respiratory Distress Syndrome in Patients With COVID-19 in the Intensive Care Unit: Retrospective Analysis**. JMIR public health and surveillance. 2021;7(3):e24843.	No ventilation outcomes
Zhang Q, Shen J, Chen L, Li S, Zhang W, Jiang C, et al. **Timing of invasive mechanic ventilation in critically ill patients with coronavirus disease 2019**. The journal of trauma and acute care surgery. 2020;89(6):1092-8	No ventilation outcomes
Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Adalia R, et al. **Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study**. Critical care (London, England). 2020;24(1):597	Wrong comparator (proning)

General ventilation search

Reference	Reason for Exclusion
Wats K, Rodriguez D, Sadiq A, Goldberger M, Moskovits M, Shani J, et al. **Association of right ventricular dysfunction and pulmonary hypertension with adverse 30-day outcomes in COVID-19 patients**. Pulmonary Circulation. 2021;11(2).	No ventilation outcomes
Hussein MH, Toraih EA, Attia AS, Burley N, Zhang AD, Roos J, et al. **Asthma in COVID-19 patients: An extra chain fitting around the neck?** Respiratory medicine. 2020;175:106205	No ventilation outcomes
Owusu D, Kim L, O'Halloran A, Whitaker M, Piasecki AM, Reingold A, et al. **Characteristics of Adults Aged 18–49 Years Without Underlying Conditions Hospitalized With Laboratory-Confirmed Coronavirus Disease 2019 in the United States: COVID-NET—March–August 2020**. Clinical Infectious Diseases. 2021;72(5):e162-e6.	No ventilation outcomes
Anesi GL, Jablonski J, Harhay MO, Atkins JH, Bajaj J, Baston C, et al. **Characteristics, Outcomes, and Trends of Patients With COVID-19-Related Critical Illness at a Learning Health System in the United States**. Annals of internal medicine. 2021;174(5):613-21	No ventilation outcomes
Thomson RJ, Hunter J, Dutton J, Schneider J, Khosravi M, Casement A, et al. **Clinical characteristics and outcomes of critically ill patients with COVID-19 admitted to an intensive care unit in London: A prospective observational cohort study**. PloS one. 2020;15(12):e0243710	No ventilation outcomes
Lian Y, Hou G, Xie W, Zhong Z, Huang K, Li G, et al. **Clinical characteristics and prognosis of COVID-19 patients with tracheal intubation**. International Journal of Clinical and Experimental Medicine. 2021;14(5):1911-8.	No NIV outcomes
Gavin W, Campbell E, Zaidi S-A, Gavin N, Dbeibo L, Beeler C, et al. **Clinical characteristics, outcomes and prognosticators in adult patients hospitalized with COVID-19**. American journal of infection control. 2021;49(2):158-65	No NIV outcomes
Serafim RB, Povoa P, Souza-Dantas V, Kalil AC, Salluh JIF. **Clinical course and outcomes of critically ill patients with COVID-19 infection: a systematic review**. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2021;27(1):47-54.	No NIV outcomes
Zhou S, Yang Y, Zhang X, Li Z, Liu X, Hu C, et al. **Clinical Course of 195 Critically Ill COVID-19 Patients: A Retrospective Multicenter Study**. Shock (Augusta, Ga). 2020;54(5):644-51.	No NIV outcomes
Mody A, Lyons PG, Guillamet CV, Michelson A, Yu S, Namwase AS, et al. **The Clinical Course of Coronavirus Disease 2019 in a US Hospital System: A Multistate Analysis**. American Journal of Epidemiology. 2021;190(4):539-52.	No NIV outcomes

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Lin DD, Wu Y, Toom S, Becker K, Burdette-Radoux S, D'Silva J, et al. **Clinical Determinants Differentiating the Severity of SARS-CoV-2 Infection in Cancer Patients: Hospital Care or Home Recovery**. Frontiers in Medicine. 2021;8:604221.	No ventilation outcomes
Wang J, Zheng X, Chen J. **Clinical progression and outcomes of 260 patients with severe COVID-19: an observational study**. Scientific reports. 2021;11(1):3166	No ventilation outcomes
Wunsch H, Hill AD, Bosch N, Adhikari NKJ, Rubenfeld G, Walkey A, et al. **Comparison of 2 Triage Scoring Guidelines for Allocation of Mechanical Ventilators**. JAMA network open. 2020;3(12):e2029250	No outcomes
Velissaris D, Aretha D, Tsiotsios K, Gogos C, Karamouzos V. **Continuous positive airway pressure in the treatment of COVID-19 patients with respiratory failure. A report of six cases with excellent outcome**. Advances in Respiratory Medicine. 2021;89(2):197-202.	Not RCT
Raimondi F, Novelli L, Ghirardi A, Russo FM, Pellegrini D, Biza R, et al. **Covid-19 and gender: lower rate but same mortality of severe disease in women-an observational study**. BMC pulmonary medicine. 2021;21(1):96	No ventilation outcomes
Da Silva JF, Browning SD, Bruce BB, Natarajan P, Rogers-Brown J, Gold JAW, et al. **COVID-19 Clinical Phenotypes: Presentation and Temporal Progression of Disease in a Cohort of Hospitalized Adults in Georgia, United States**. Open Forum Infectious Diseases. 2021;8(1):ofaa596	No ventilation outcomes
Uggeri S, Gilioli F, Cosenza R, Moreali S, Nasi F, Guicciardi N. **COVID-19 pneumonia: A tailor-made dress for a down syndrome patient**. Italian Journal of Medicine. 2021;15(1):59-63	Case report (n=1)
Sykes D, Parthasarthy A, Brown O, Crooks M, Faruqi S. **COVID-19 progression, frailty, and use of prolonged continuous positive airway pressure as a ward-based treatment: Lessons to be learnt from a case**. Lung India. 2021;38(7 Supplement 1):S64-S8.	Case report (n=1)
Massabeti R, Cipriani MS, Valenti I. **Covid-19: A systemic disease treated with a wide-ranging approach: A case report**. Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharmacologie clinique. 2020;27(S Pt 1):e26-e30.	Case report n=1
Arabi YM, Fowler R, Hayden FG. **Critical care management of adults with community-acquired severe respiratory viral infection**. Intensive care medicine. 2020;46(2):315-28	Narrative review
Gupta RK, Harrison EM, Ho A, Docherty AB, Knight SR, van Smeden M, et al. **Development and validation of the ISARIC 4C Deterioration model for adults hospitalised with COVID-19: a prospective cohort study**. The Lancet Respiratory medicine. 2021;9(4):349-59.	No ventilation outcomes
Dorgham K, Quentric P, Gokkaya M, Marot S, Parizot C, Sauce D, et al. **Distinct cytokine profiles associated with COVID-19 severity and mortality**. The Journal of allergy and clinical immunology. 2021;147(6):2098-107.	No ventilation outcomes
Lu G, Wang J. **Dynamic changes in routine blood parameters of a severe COVID-19 case**. Clinica chimica acta; international journal of clinical chemistry. 2020;508:98-102	Case report (n=1)
Tiwari-Heckler S, Rauber C, Merle U, Longhi MS, Zornig I, Jager D, et al. **Dysregulated Host Response in Severe Acute Respiratory Syndrome Coronavirus 2-Induced Critical Illness**. Open Forum Infectious Diseases. 2021;8(3).	No ventilator outcomes
Elgamasy S, Sakr EE, Kamel MG, Ghozy S, Elsayed GG, Nagaty Ibrahim MM, et al. **Epidemiologic features and clinical course of COVID-19: A retrospective analysis of 19 patients in Germany**. Future Virology. 2021;16(3):191-9.	No ventilation outcomes
Hur K, Price CPE, Gray EL, Gulati RK, Maksimoski M, Racette SD, et al. **Factors Associated With Intubation and Prolonged Intubation in Hospitalized Patients With COVID-19**. Otolaryngology-Head & Neck Surgery. 2020;163(1):170-8.	No ventilation outcomes

Laverdure F, Delaporte A, Bouteau A, Genty T, Decailliot F, Stéphan F. **Impact of initial respiratory compliance in ventilated patients with acute respiratory distress syndrome related to COVID-19**. BioMed Central; 2020. p. 1-4.	No NIV outcomes
Zheng H, Tan J, Zhang X, Luo A, Wang L, Zhu W, et al. **Impact of sex and age on respiratory support and length of hospital stay among 1792 patients with COVID-19 in Wuhan, China**. New York, New York: Elsevier B.V.; 2020. p. e378-e80	No outcomes from ventilation
Mojon D, Calvo A, Izquierdo A, Belarte-Tornero L, Salvatella N, Llagostera M, et al. **Influence of cardiovascular disease and cardiovascular risk factors in COVID-19 patients. Data from a large prospective Spanish cohort**. REC: CardioClinics. 2021;56(2):108-17.	No ventilation outcomes
Chang MC, Kim TU, Park D. **National early warning score on admission as risk factor for invasive mechanical ventilation in COVID-19 patients: A STROBE-compliant study**. Medicine. 2021;100(19):e25917.	No NIV outcomes
Perkins R, Ingebretson E, Holifield L, Bergeron A. A Nurse's Guide to COVID-19. The American journal of nursing. 2021;121(3):28-38.	Narrative review
Memtsoudis SG, Ivascu NS, Pryor KO, Goldstein PA. **Obesity as a risk factor for poor outcome in COVID-19-induced lung injury: the potential role of undiagnosed obstructive sleep apnoea**. New York, New York: Elsevier B.V.; 2020. p. e262-e3.	No NIV outcomes
Varadaraj P, Gopalan S, Nair AM, Marappa L, Rajendran V, Pandurangan V, et al. **Outcomes in severe sars-cov-2 patients with liberal oxygenation and steroid therapy-a single centre experience**. Critical Care and Shock. 2021;24(3):130-4	No NIV comparisons
Gresser E, Rueckel J, Puhr-Westerheide D, Schwarze V, Fink N, Kunz WG, et al. **Prognostic value of admission chest ct findings for invasive ventilation therapy in covid-19 pneumonia**. Diagnostics. 2020;10(12):1108.	No ventilation outcomes
Heim M, Kriescher S, Berg-Johnson W, Fuest K, Kapfer B, Schneider G, et al. **Rapid clinical evolution for COVID-19 translates into early hospital admission and unfavourable outcome: A preliminary report**. Multidisciplinary Respiratory Medicine. 2021;16:744	No ventilation outcomes
Schreyer KE, Isenberg DL, Satz WA, Lucas NV, Rosenbaum J, Zandrow G, et al. **Rate of Decompensation of Normoxic Emergency Department Patients with SARS-CoV-2**. The western journal of emergency medicine. 2021;22(3):580-6.	No ventilation outcomes
Rauseo M, Mirabella L, Caporusso RR, Cantatore LP, Perrini MP, Vetuschi P, et al. **SARS-CoV-2 pneumonia succesfully treated with cpap and cycles of tripod position: a case report**. BMC Anesthesiology. 2021;21(1):1-4.	Case report (n=1)
Raheja H, Chukwuka N, Agarwal C, Sharma D, Munoz-Martinez A, Fogel J, et al. **Should COVID-19 patients >75 years be Ventilated? An Outcome Study**. QJM : monthly journal of the Association of Physicians. 2021;114(3):182-9	No ventilation outcomes
Kayem G, Lecarpentier E, Deruelle P, Bretelle F, Azria E, Blanc J, et al. **A snapshot of the Covid-19 pandemic among pregnant women in France**. Journal of gynecology obstetrics and human reproduction. 2020;49(7):101826	No ventilation outcomes
Bos LDJ, Paulus F, Vlaar APJ, Beenen LFM, Schultz MJ. **Subphenotyping Acute Respiratory Distress Syndrome in Patients with COVID-19: Consequences for Ventilator Management**. New York, New York: American Thoracic Society; 2020. p. 1161-3.	No ventilation outcomes
Pedigo R. **Ventilator management of adult patients in the emergency department**. Emergency medicine practice. 2020;22(7):1-20.	Narrative review / commentary

NIV_Covid_Hypoxemia

Reference	Reason for exclusion

Arabi YM, Fowler R, Hayden FG. **Critical care management of adults with community-acquired severe respiratory viral infection**. Intensive care medicine. 2020;46(2):315-28	Narrative review
Ashish A, Unsworth A, Martindale J, Sundar R, Kavuri K, Sedda L, et al. **CPAP management of COVID-19 respiratory failure: a first quantitative analysis from an inpatient service evaluation**. BMJ open respiratory research. 2020;7(1).	Not RCT
Bastoni D, Poggiali E, Demichele E, Tinelli V, Iannicelli T, Magnacavallo A, et al. **Prone positioning in patients treated with non-invasive ventilation for COVID-19 pneumonia in an Italian emergency department**. Emergency Medicine Journal. 2020(9):565-6.	Not RCT
Brusasco C, Corradi F, Di Domenico A, Raggi F, Timossi G, Santori G, et al. **Continuous positive airway pressure in COVID-19 patients with moderate-to-severe respiratory failure**. The European respiratory journal. 2021;57(2)	Not RCT
Cammarota G, Rossi E, Vitali L, Simonte R, Sannipoli T, Anniciello F, et al. **Effect of awake prone position on diaphragmatic thickening fraction in patients assisted by noninvasive ventilation for hypoxemic acute respiratory failure related to novel coronavirus disease**. Critical care (London, England). 2021;25(1):305.	NIV incidental, not RCT
Cena T, Bazzano S, Perucca R, Cammarota G, Vaschetto R, Barone-Adesi F, et al. **Outcomes of covid-19 patients treated with continuous positive airway pressure outside the intensive care unit**. ERJ Open Research. 2021;7(1):1-8	Not RCT
Coppadoro A, Benini A, Fruscio R, Verga L, Mazzola P, Bellelli G, et al. **Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak**. Critical care (London, England). 2021;25(1):80.	Not RCT
Corradi F, Vetrugno L, Orso D, Bove T, Schreiber A, Boero E, et al. **Diaphragmatic thickening fraction as a potential predictor of response to continuous positive airway pressure ventilation in Covid-19 pneumonia: A single-center pilot study**. Respiratory physiology & neurobiology. 2021;284:103585.	Not RCT
Delorme M, Leroux K, Boussaid G, Lebret M, Prigent H, Leotard A, et al. **Protective Recommendations for Non-invasive Ventilation During COVID-19 Pandemic: A Bench Evaluation of the Effects of Instrumental Dead Space on Alveolar Ventilation**. Archivos de bronconeumologia. 2021;57 Suppl 2:28-33	Bench study (non-clinical)
Fakhri S, Balaban E, Hippensteel JA, Jolley S, Sippel J, Peterson R, et al. **Assessing the use of heated high flow nasal cannula in COVID-19**. American Journal of Respiratory and Critical Care Medicine. 2021;203(9).	Poster abstract
Faraone A, Beltrame C, Crociani A, Carrai P, Lovicu E, Filetti S, et al. **Effectiveness and safety of noninvasive positive pressure ventilation in the treatment of COVID-19-associated acute hypoxemic respiratory failure: a single center, non-ICU setting experience**. Internal and emergency medicine. 2021;16(5):1183-90	Not RCT
Forrest IS, Do R, Jaladanki SK, Paranjpe I, Glicksberg BS, Nadkarni GN. **Non-invasive ventilation versus mechanical ventilation in hypoxemic patients with COVID-19**. Infection. 2021	NIV undefined
Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. **Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia**. The European respiratory journal. 2020;56(5	Wrong comparator
Gough C, Casey M, McCartan TA, Franciosi AN, Nash D, Doyle D, et al. **Effects of non-invasive respiratory support on gas exchange and outcomes in COVID-19 outside the ICU**. Respiratory medicine. 2021;185:106481	Wrong comparator
Grieco DL, Menga LS, Cesarano M, Rosa T, Spadaro S, Bitondo MM, 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**	Wrong intervention (Helmet CPAP)

Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. JAMA. 2021;325(17):1731-43	
Groff P, Ferrari R. **Non-invasive respiratory support in the treatment of acute hypoxemic respiratory failure secondary to CoViD-19 related pneumonia**. European Journal of Internal Medicine. 2021;86:17-21.	Narrative review
Guenancia TN, Rosa A, Damoisel C, Mercier FJ, Jeannin B. **Implementation of a non-invasive oxygenation support strategy during the COVID-19 pandemic in an ephemeral Respiratory Intermediate Care Unit**. Anaesthesia, critical care & pain medicine. 2020;39(4):459-60	Description of process, no outcomes
Karamouzos V, Fligou F, Gogos C, Velissaris D. **High flow nasal cannula oxygen therapy in adults with COVID-19 respiratory failure. A case report**. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace. 2020;90(2).	Case report (n=1)
Mateos-Rodriguez A, Ortega-Anselmi J, Candel-Gonzalez FJ, Canora-Lebrato J, Fragiel-Saavedra M, Hernandez-Piriz A, et al. **[Alternative CPAP methods for the treatment of secondary serious respiratory failure due to pneumonia by COVID-19]**. Metodos alternativos de CPAP para el tratamiento de insuficiencia respiratoria grave secundaria a neumonia por COVID-19. 2021;156(2):55-60	Spanish
Matute-Villacis M, Armas J, Fernandez I, Medina M, Moises J, Embid C, et al. **Role of respiratory intermediate care units during the SARS-CoV-2 pandemic**. BMC Pulmonary Medicine. 2021;21(1):228.	RICU, not ventilation
Menzella F, Barbieri C, Fontana M, Scelfo C, Castagnetti C, Ghidoni G, et al. **Effectiveness of noninvasive ventilation in COVID-19 related-acute respiratory distress syndrome**. Clinical Respiratory Journal. 2021;15(7):779-87.	Not RCT
Mukhtar A, Lotfy A, Hasanin A, El-Hefnawy I, El Adawy A. **Outcome of non-invasive ventilation in COVID-19 critically ill patients: A Retrospective observational Study**. Anaesthesia, critical care & pain medicine. 2020;39(5):579-80.	Not RCT
Peng M, Li R, Cao W, Li W, Wu M, Lyu Y, et al. **A critical COVID-19 patient managed with timely evaluation, early prone positioning ventilation, and a multi-pronged pharmacotherapy**. European Journal of Inflammation. 2021;19	Case report (n=1)
Raharja A, Kwan JTC, Billings JJ, Aminy-Raouf H, Lohani S, Khan B, et al. **Ward-based continuous positive airway pressure (CPAP) in SARS-CoV-2**. Clinical Medicine. 2021;21:55-6.	Not RCT
Rama-Maceiras P, Pita E, Blanco P, Ramos L, Sanduende Y, Varela M, et al. **Critical patients COVID-19 has changed the management and outcomes in the ICU after 1 year of the pandemic? A multicenter, prospective, observational study**. Enfermedades Infecciosas y Microbiologia Clinica. 2021.	Spanish
Retucci M, Aliberti S, Ceruti C, Santambrogio M, Tammaro S, Cuccarini F, et al. **Prone and Lateral Positioning in Spontaneously Breathing Patients With COVID-19 Pneumonia Undergoing Noninvasive Helmet CPAP Treatment**. Chest. 2020;158(6):2431-5.	Wrong intervention (Helmet CPAP)
Sargent W, Ali S, Kukran S, Harvie M, Soin S. **The prognostic value of chest X-ray in patients with COVID-19 on admission and when starting CPAP**. Clinical Medicine. 2021;21(1):e14-e9.	Not RCT, no ventilation outcomes
Sykes D, Parthasarthy A, Brown O, Crooks M, Faruqi S. **COVID-19 progression, frailty, and use of prolonged continuous positive airway pressure as a ward-based treatment: Lessons to be learnt from a case**. Lung India. 2021;38(7 Supplement 1):S64-S8	Case report (n=1)
Talbot J, Raste Y, Vijayasingam A, Breck S. **Lessons learnt from the use of CPAP for patients with type 1 respiratory failure due to COVID-19 pneumonia in a district general hospital outside a critical care setting**. Clinical Medicine. 2021;21:19-20	Not RCT

Velissaris D, Aretha D, Tsiotsios K, Gogos C, Karamouzos V. **Continuous positive airway pressure in the treatment of COVID-19 patients with respiratory failure. A report of six cases with excellent outcome**. Advances in Respiratory Medicine. 2021;89(2):197-202.	Small case series (n=6)
Voshaar T, Stais P, Kohler D, Dellweg D. **Conservative management of covid-19 associated hypoxaemia**. ERJ Open Research. 2021;7(1):00026-2021	Not RCT
Winearls S, Swingwood EL, Hardaker CL, Smith AM, Easton FM, Millington KJ, et al. **Early conscious prone positioning in patients with COVID-19 receiving continuous positive airway pressure: a retrospective analysis**. BMJ open respiratory research. 2020;7(1)	Wrong comparator (proning), not RCT
Colaianni-Alfonso N, Montiel G, Castro-Sayat M, Siroti C, Vega ML, Toledo A, et al. **Combined non-invasive respiratory support therapies to treat SARS-CoV-2 patients: A prospective Observational Study**. Respiratory care. 2021.	Not RCT

Search Strategy

Search 1: HHHFO

Database: Ovid MEDLINE(R) ALL <1946 to July 27, 2021>

Search Strategy:

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1 COVID-19/ or SARS-CoV-2/ or Coronavirus/ or Betacoronavirus/ or Coronavirus Infections/ (101869)

2 exp Oxygen/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (10826)

3 exp Oxygen Inhalation Therapy/mt, st, sn, th [Methods, Standards, Statistics & Numerical Data, Therapy] (5508)

4 exp Respiratory Insufficiency/th [Therapy] (17135)

5 exp Respiratory Distress Syndrome/th [Therapy] (12221)

6 exp Noninvasive Ventilation/is, mt [Instrumentation, Methods] (1183)

7 exp Cannula/ (1134)

8 "high-flow oxygen".ti,ab. (622)

9 airvo.ti,ab. (12)

10 optiflow.ti,ab. (55)

11 Vapotherm.ti,ab. (32)

12 "high-flow nasal cannula".ti,ab. (1324)

13 "high-flow nasal oxygen".ti,ab. (268)

14 or/2-13 (45582)

15 1 and 14 (1122)

16 exp Treatment Outcome/ (1128781)

17 exp Disease Progression/ (192863)

18 exp Time Factors/ (1212142)

19 exp "Severity of Illness Index"/ (267175)

20 exp "Length of Stay"/ (94610)

21 exp Risk Assessment/ (289008)

22 exp Monitoring, Physiologic/ (183070)

23 exp Biomarkers/an, bl [Analysis, Blood] (324575)

24 or/16-23 (3162803)

25 15 and 24 (402)

26 limit 25 to (english language and humans and yr="2020 -Current") (387)

27 limit 26 to ("all adult (19 plus years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (304)
28 limit 27 to (clinical trial or comparative study or controlled clinical trial or evaluation study or guideline or journal article or meta analysis or multicenter study or observational study or practice guideline or randomized controlled trial or "scientific integrity review" or "systematic review") (256)
29 remove duplicates from 28 (254)

Database: Embase <1996 to 2021 Week 29>
Search Strategy:
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1 COVID-19/ or SARS-CoV-2/ or coronavirinae/ or betacoronavirus/ or Coronavirus infection/ (32310)
2 exp Oxygen/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (991)
3 exp Oxygen Inhalation Therapy/ (64247)
4 exp Respiratory Insufficiency/th [Therapy] (13124)
5 exp noninvasive ventilation/ (14930)
6 exp cannula/ (19771)
7 exp oxygen therapy/ (64247)
8 "high-flow oxygen".ti,ab. (1229)
9 Airvo.ti,ab. (64)
10 Optiflow.ti,ab. (178)
11 Vapotherm.ti,ab. (105)
12 "high-flow nasal cannula".ti,ab. (2374)
13 "high-flow nasal oxygen".ti,ab. (458)
14 or/2-13 (102440)
15 exp treatment outcome/ (1804695)
16 exp disease exacerbation/ (137146)
17 exp time factor/ (40474)
18 exp disease severity/ (1768868)
19 exp "length of stay"/ (206737)
20 exp risk assessment/ (600593)
21 or/15-20 (3945183)
22 1 and 14 (1012)
23 21 and 22 (483)

24 limit 23 to (human and english language and yr="2020 -Current") (455)
25 limit 24 to exclude medline journals (114)
26 limit 25 to (adult <18 to 64 years> or aged <65+ years>) (83)
27 remove duplicates from 26 (83)

CINAHL

#	Query	Results
S20	S9 AND S17	41
S19	S9 AND S17	82
S18	S9 AND S17	89
S17	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	837,925
S16	(MH "Time Factors")	179,060
S15	(MH "Length of Stay")	45,920
S14	(MH "Risk Assessment")	118,345
S13	(MH "Outcomes (Health Care)+")	523,748
S12	(MH "Treatment Outcomes+") OR (MH "Outcome Assessment")	440,772
S11	(MH "Severity of Illness")	31,225
S10	(MH "Disease Progression+")	50,817
S9	S1 AND S8	251
S8	S2 OR S3 OR S4 OR S5 OR S6 OR S7	12,741
S7	"vapotherm"	39
S6	"optiflow"	31
S5	"airvo"	10
S4	(MH "Oxygen Delivery Devices+") OR "high flow oxygen"	3,865
S3	(MH "Nasal Cannula")	606
S2	(MH "Oxygen Therapy+")	9,508
S1	(MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR COVID-19 OR COVID19 OR COVID-2019 OR	65,353

COVID2019 OR SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019 OR "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*" OR "2019 ncov" OR 2019ncov OR Hcov*

Search 2: Ventilators

Database: Ovid MEDLINE(R) ALL <1946 to July 27, 2021>
Search Strategy:

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1 COVID-19/ or SARS-CoV-2/ or Coronavirus/ or Betacoronavirus/ or Coronavirus Infections/ (101869)
2 exp Disease Progression/ (192863)
3 exp "Severity of Illness Index"/ (267175)
4 exp Risk Assessment/ (289008)
5 exp Respiration, Artificial/ (81981)
6 exp Ventilators, Mechanical/ (9562)
7 exp Intubation, Intratracheal/ (40422)
8 or/5-7 (120917)
9 1 and 8 (2548)
10 or/2-4 (699129)
11 9 and 10 (452)
12 limit 11 to (english language and humans and yr="2020 -Current") (446)
13 limit 12 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (339)
14 limit 13 to (case reports or clinical trial or comparative study or controlled clinical trial or evaluation study or guideline or meta analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or "review" or "scientific integrity review" or "systematic review") (179)

Database: Embase <1996 to 2021 Week 29>
Search Strategy:

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1 COVID-19/ or SARS-CoV-2/ or coronavirinae/ or betacoronavirus/ or Coronavirus infection/ (32310)
2 exp treatment outcome/ (1804695)
3 exp disease exacerbation/ (137146)
4 exp disease severity/ (1768868)
5 exp risk assessment/ (600593)
6 or/2-5 (3798019)
7 exp artificial ventilation/ (172790)
8 exp mechanical ventilator/ (4568)
9 exp endotracheal intubation/ (44377)
10 or/7-9 (205281)
11 1 and 10 (1719)
12 6 and 11 (776)
13 limit 12 to (human and english language and yr="2020 -Current") (729)
14 limit 13 to exclude medline journals (163)
15 limit 14 to (adult <18 to 64 years> or aged <65+ years>) (109)

CINAHL

#	Query	Results
S18	S9 AND S14	128
S17	S9 AND S14	275
S16	S9 AND S14	295
S15	S9 AND S14	299
S14	S1 AND S13	1,039
S13	S10 OR S11 OR S12	50,351
S12	(MH "Intubation, Intratracheal+")	15,621
S11	(MH "Ventilators, Mechanical")	3,171
S10	(MH "Respiration, Artificial+")	35,799
S9	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	837,925
S8	(MH "Time Factors")	179,060
S7	(MH "Length of Stay")	45,920
S6	(MH "Risk Assessment")	118,345
S5	(MH "Outcomes (Health Care)+")	523,748
S4	(MH "Treatment Outcomes+") OR (MH "Outcome Assessment")	440,772
S3	(MH "Severity of Illness")	31,225
S2	(MH "Disease Progression+")	50,817
S1	(MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR COVID-19 OR COVID19 OR COVID-2019 OR COVID2019 OR SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019 OR "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*" OR "2019 ncov" OR 2019ncov OR Hcov*	65,353

Search 3: NIV

Database: Ovid MEDLINE(R) ALL <1946 to September 10, 2021>
Search Strategy:
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1 COVID-19/ or SARS-CoV-2/ or Coronavirus/ or Betacoronavirus/ or Coronavirus Infections/ (111533)
2 exp Treatment Outcome/ (1139224)
3 exp Disease Progression/ (194351)
4 exp Time Factors/ (1214954)
5 exp "Severity of Illness Index"/ (269119)
6 exp "Length of Stay"/ (95490)
7 exp Risk Assessment/ (291461)
8 effect*.ti. (2072468)
9 exp Monitoring, Physiologic/ (184240)
10 exp Biomarkers/an, bl [Analysis, Blood] (326457)
11 or/2-10 (4994814)
12 exp Continuous Positive Airway Pressure/ or CPAP.ti. (9064)
13 "Bilevel Positive Airway Pressure".ti. (85)
14 exp Noninvasive Ventilation/ (2809)
15 or/12-14 (11633)
16 1 and 11 and 15 (95)
17 limit 16 to (english language and humans and ("all adult (19 plus years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")) (69)
18 limit 17 to (english language and yr="2020 -Current") (67)

Database: Embase <1996 to 2021 Week 36>
Search Strategy:
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1 COVID-19/ or SARS-CoV-2/ or Coronavirus/ or Betacoronavirus/ or Coronavirus Infections/ (38022)
2 exp Treatment Outcome/ (1825538)
3 exp Disease Progression/ (140131)
4 exp Time Factors/ (41296)
5 exp "Severity of Illness Index"/ (19322)
6 exp "Length of Stay"/ (209577)
7 exp Risk Assessment/ (607793)
8 effect*.ti. (1676845)
9 exp Monitoring, Physiologic/ (7706)
10 exp Biomarkers/an, bl [Analysis, Blood] (8456)
11 or/2-10 (4153429)
12 exp Continuous Positive Airway Pressure/ or CPAP.ti. (7839)

13 "Bilevel Positive Airway Pressure".ti. (114)
14 exp Noninvasive Ventilation/ (15501)
15 or/12-14 (22456)
16 1 and 11 and 15 (165)
17 limit 16 to (english language and humans and ("all adult (19 plus years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")) [Limit not valid in Embase; records were retained] (163)
18 limit 17 to (english language and yr="2020 -Current") (162)

CINAHL

#	Query	Results
S20	S1 AND S4	21
S19	S1 AND S5 AND S16	18
S18	S1 AND S5 AND S16	18
S17	S1 AND S5 AND S16	20
S16	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	1,302,637
S15	TI effect*	357,907
S14	(MH "Mortality+")	77,430
S13	(MH "Morbidity+")	178,537
S12	(MH "Disease Progression+")	51,149
S11	(MH "Severity of Illness")	31,437
S10	(MH "Treatment Outcomes+") OR (MH "Outcome Assessment")	442,971
S9	(MH "Outcomes (Health Care)+")	526,278
S8	(MH "Risk Assessment")	119,437
S7	(MH "Length of Stay")	45,665
S6	(MH "Time Factors")	179,115
S5	S2 OR S3 OR S4	6,543
S4	TI noninvasive ventilation	1,055
S3	TI bilevel positive airway pressure	37
S2	(MH "Continuous Positive Airway Pressure")	5,591

S1	(MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR COVID-19 OR COVID19 OR COVID-2019 OR COVID2019 OR SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019 OR "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*" OR "2019 ncov" OR 2019ncov OR Hcov*	70,437