High flow nasal oxygen therapy compared with conventional oxygen therapy in hospitalised patients with respiratory illness: a systematic review and meta-analysis

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Research Article

Keywords: Acute respiratory failure, chronic respiratory disease, oxygen therapy, high flow nasal oxygen, mortality, ventilation, coronavirus-19, chronic obstructive pulmonary disease

Posted Date: January 24th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2408451/v1

Abstract

Background

This systematic review aims to summarise the evidence regarding any benefits of high flow nasal oxygen (HFNO) therapy compared to conventional oxygen therapy (COT) in hospitalised patients with acute or chronic respiratory illnesses.

Methods

A comprehensive search was performed across three databases for studies that reported any of: escalation to invasive mechanical ventilation (IMV), mortality, length of stay, carbon dioxide levels, disability, or admission rates.

Results

In patients with acute respiratory illnesses, pooled RCT data revealed no significant differences between HFNO and COT in overall need for IMV (RR = 0.82, 95% CI = 0.65–1.05; p = 0.11; n = 15 RCTs) or in-hospital mortality (RR = 1.00, 95% CI 0.85–1.17; p = 1.00; n = 5). Similarly, for patients with chronic respiratory illnesses, RCT data revealed no significant difference in overall need for IMV (RR = 0.86, 95% CI = 0.33–2.23; p = 0.76; n = 4) or in-hospital mortality (RR = 0.40, 95% CI = 0.04–4.10; p = 0.44; n = 1) for HFNO compared to COT. Patients with COVID-19 receiving HFNO had a significantly reduced need for IMV (RR = 0.72, 95% CI = 0.63–0.82; p < 0.001), short-term mortality (RR = 0.62, 95% CI = 0.48–0.79; p < 0.001), and long-term mortality (RR = 0.67, 95% CI = 0.48–0.92; p = 0.01).

Conclusion

HFNO did not significantly reduce the need for IMV escalation or in-hospital mortality in patients with acute or chronic respiratory illnesses, except for patients with COVID-19.

Take Home Message

HFNO did not significantly reduce the overall need for IMV escalation in hospitalised patients with acute respiratory illnesses (RR=0.82, 95% CI=0.65-1.05; p=0.11), or with chronic respiratory illnesses (RR=0.86, 95% CI=0.33-2.23; p=0.76) compared to COT.

Background

High flow nasal oxygen (HFNO) therapy delivers humidified heated oxygen at flow rates of up to 60L/min(1). HFNO has several advantages over conventional oxygen therapy (COT) that is delivered via

traditional nasal cannula or face mask, including reliable fraction of inspired oxygen (FiO_2) delivery(2), improved breathing pattern(3–5), increased airway secretion clearance, and greater patient comfort(6–8). Additional physiological benefits of HFNO include upper airway dead space washout and generation of positive end expiratory pressure at approximately 1cmH_2O for every 10L/min of flow(2), which contributes to decreased work of breathing and improved oxygenation(1, 7, 9).

Although systematic reviews have examined the benefits of HFNO compared to COT in patients with acute respiratory failure (ARF) in recent years(10–26), these have included randomised controlled trials (RCTs) only and focused on HFNO use in intensive care units (ICUs). Additionally, most reviews were conducted before the coronavirus disease (COVID-19) pandemic due to the SARS-CoV-2 virus. With increasing adoption of HFNO within multiple hospital settings (emergency departments (EDs), ward areas, high dependency units and ICUs) globally due to a surge of patients with ARF secondary to COVID-19(27), there is a pressing need to review the evidence for using HFNO in multiple hospital settings. Of note, several new studies have been published since 2020 comparing HFNO to COT in patients with COVID-19(28–33). This updated systematic review and meta-analysis aimed to comprehensively include new data from RCTs and observational studies across a broad range of patients with acute and chronic respiratory illnesses in varied hospital settings (ICU, ED, and hospital wards) to determine whether HFNO led to improved clinical outcomes compared to COT in this population.

Methods And Materials

Search Strategy and study selection

A comprehensive search was performed on the 29th June 2021 for articles within the last 50 years across Embase, Medline via Ovid, and CENTRAL databases. Keywords employed included “exp Oxygen Inhalation therapy/”, “Oxygen* adj4 therap*”, “high*-flow* adj45 nasal”, “high*- flow* adj5 oxygen*”, AND Mesh terms for a range of acute and chronic respiratory illnesses. The full search strategy can be found in Supplementary Tables 1a-1c. The study protocol was registered with PROSPERO (CRD42021264837).

To meet inclusion criteria for this review, studies had to evaluate HFNO in hospitalised adult patients (≥ 18 years) with either an acute respiratory illness, or a prior diagnosis of chronic respiratory illness and a need for respiratory support therapy. RCTs, crossover studies, and observational studies with an intervention and comparator group were included. Hospitalisation was defined as ED presentation, or admission to an ICU or ward. HFNO was defined as flow rates > 20L/min delivered via specialised high flow devices and nasal cannulae. COT was defined as flow rates ≤ 15L/min delivered via standard nasal cannulae, simple face mask, non-rebreather reservoir mask, or venturi mask. Acute respiratory illnesses included acute respiratory failure (with or without hypercapnia), upper and lower respiratory tract infections, COVID-19, acute respiratory distress syndrome, acute exacerbations of a chronic respiratory illness, pulmonary embolism, pneumothorax, acute lung injury, and transfusion-related acute lung Injury. Chronic respiratory illnesses were defined as a past diagnosis of any of: COPD, interstitial lung disease, asthma, cystic fibrosis, bronchiectasis, obesity hypoventilation syndrome, chronic respiratory failure from

neuromuscular disease, lung transplantation, pulmonary hypertension, and lung or pleural malignancy. Studies examining patients with chronic respiratory illnesses without a concurrent acute respiratory illness were excluded from the chronic respiratory illness group. Studies with participants with acute on chronic respiratory illness were included in both of the separate analyses for people with acute respiratory illness and those with chronic respiratory disease.

The primary outcome of interest was the need for escalation of therapy to invasive ventilation (IMV), while secondary outcomes included: mortality (hospital, short-term at ≤ 30 days, and long-term at > 30 days), escalation of therapy to non-invasive ventilation (NIV), ICU and hospital length of stay (LOS), changes in partial pressure of carbon dioxide ($PaCO_2$) levels, disability as defined by study authors (for example: dyspnoea scores), and inpatient admission rates for studies evaluating patients in ED. Studies with patients under 18 years old, comparisons of HFNO to NIV or IMV only, evaluations of domiciliary oxygen therapy, or written in languages other than English were excluded.

Data extraction

Two independent reviewers (DS, YK, SK, DMS, YN or NS) screened abstracts and full-text articles sequentially in pairs for eligible studies. A third reviewer (YK or NS) resolved disagreements between reviewer pairs by adjudication. For each included study, the risk of bias was assessed independently by two authors (DS and SK) with adjudication by a third author (YK) or consensus after discussion. RCTs and randomised crossover studies were assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), while non-randomised interventional studies were assessed using the ROBINS-I framework. The Newcastle-Ottawa Scale was used for assessments of observational studies.

Data synthesis

Treatment effects were pooled using the random effects model as this would weigh the heterogeneous studies more equally than the fixed effects model. Mantel-Haenszel method was employed for dichotomous outcomes, while inverse variance weighting method was used for continuous outcomes. I^2 statistic values were used to assess for heterogeneity with the following thresholds: low (25–49%), moderate (50–74%), and high (≥ 75%). Treatment effects were expressed as mean difference (with 95% confidence intervals (CI)) for continuous outcomes and risk ratio (RR) (with 95% CI) for dichotomous outcomes. For the primary analyses, we pooled data from RCTs only. For secondary analyses, we combined data from RCTs and observational studies to expand the body of evidence. Subgroup analyses for different types of respiratory illnesses (COPD, asthma, lung cancer, and COVID-19) and sensitivity analyses of studies with low-moderate risk of bias were performed. All meta-analyses were performed using Review Manager (RevMan, version 5.4; the Cochrane Collaboration).

Results

Of 13,689 abstracts screened, 114 abstracts from studies of patients with acute respiratory illnesses and 63 abstracts from studies of patients with chronic respiratory illnesses progressed to full-text

assessment. 52 studies (18 RCTs, 13 crossover studies, 21 observational studies) described in 63 articles for acute respiratory illnesses(3–9, 28, 30–73), and 11 studies (5 RCTs, 3 crossover studies, 3 observational studies) for patients with acute on chronic respiratory illnesses were included(63–73) (Fig. 1).

Study characteristics and quality

Characteristics of included studies for acute and chronic respiratory illnesses are available in Supplementary Tables 2–3. Pneumonia was the most common acute respiratory illness (n = 1394), while COPD was the predominant chronic respiratory illness (n = 509) for patients with an acute-on-chronic respiratory illness (Fig. 1). Definitions of respiratory illnesses, as reported by the included studies, are reflected in Supplementary Table 4.

HFNO was most commonly administered via Fisher & Paykel Optiflow™ system. The initial median flow rate for HFNO was 40L/min (range 4-60L/min) for acute respiratory illnesses and 35L/min (range 20-50L/min) for chronic respiratory illnesses. COT was initiated at a median flow rate of 11L/min (range 2-15L/min) and was most commonly delivered via nasal cannulae (Table 1).

Table 1
Characteristics of HFNO and COT delivery.

	Acute respiratory illnesses	Chronic respiratory illnesses
HFNO delivery	Flow (L/min): Median, (Range) Minimum: 13 studies, 30 (20–50) Maximum: 20 studies, 60 (40–60) Initial: 27 studies, 40 (4–60)	Flow (L/min): Median, (Range) Minimum: 3 studies, 30 (20–35) Maximum: 5 studies, 60 (50–60) Initial: 5 studies, 35 (20–50)`
	Duration < 1 hr: 8 studies 1–24 hrs: 7 studies 24–72 hrs: 3 studies > 72 hrs: 2 studies Other: 6 studies Not specified: 27 studies	Duration < 1 hr: 1 study 1–24 hrs: 2 studies Other: 3 studies Not specified: 5 studies
	HFNO system Optiflow™, Fisher & Paykel: 33 studies • AIRVO™: 2 studies • AIRVO 2™: 14 studies • AIRVO™ or AIRVO 2™: 1 study • Maxventuri: 1 study Other: 1 study Not specified: 18 studies	HFNO system Optiflow™, Fisher & Paykel: 9 studies • AIRVO™: 2 studies • AIRVO 2™: 5 studies Not specified: 2 studies
	SpO_2 target %: Median, (Range) 22 studies, ≥ 93.5 (91–96)% SPO_2 target for other studies were either expressed as a range or unspecified	SpO_2 target %: Median, (Range) 2 studies: ≥ 93 (92–94)% SPO_2 target for other studies were either expressed as a range or unspecified

*More than one system may be used for conventional oxygen therapy. HFNO: High flow nasal oxygen. COT: Conventional oxygen therapy. SpO_2: Saturation of peripheral oxygen.

	Acute respiratory illnesses	Chronic respiratory illnesses
COT delivery	Flow (L/min): Median, (Range)	Flow (L/min): Median, (Range)
	Minimum: 13 studies: 3 (1–10)	Minimum: 2 studies: 2 (2–2)
	Maximum: 12 studies: 12.5 (4–15)	Maximum: 3 studies: 10 (5–15)
	Initial: 10 studies: 11 (2–15)	Initial: 1 study: 10
	Duration	Duration
	< 1 hour: 6 studies	< 1 hour: 1 study
	1–24 hours: 7 studies	1–24 hours: 3 studies
	24 – 7 2 hours: 2 studies	Other: 1 studies
	> 72 hours: 2 studies	Not specified: 6 studies
	Other: 6 studies	
	Not specified: 29 studies	
	COT delivery*	COT delivery*
	Nasal cannula: 18 studies	Nasal cannula: 4 studies
	Face mask: 17 studies	Face mask: 3 studies
	Venturi mask: 12 studies	Venturi mask: 3 studies
	Non-rebreather mask: 14 studies	Non-rebreather mask: 2 studies
	Other: 1 study (reservoir nasal cannula)	Not specified: 2 studies
	Not specified: 10 studies	
	SpO_2 target %: Median, (Range)	SpO_2 target %: Median, (Range)
	22 studies, ≥ 93.5 (91–96)%	2 studies: ≥ 93 (92–94)%
	SPO_2 target for other studies were either expressed as a range or unspecified	SPO_2 target for other studies were either expressed as a range or unspecified

*More than one system may be used for conventional oxygen therapy. HFNO: High flow nasal oxygen. COT: Conventional oxygen therapy. SpO_2: Saturation of peripheral oxygen.

Risk of bias

Of 19 included RCTs (including 1 post-hoc analysis) for both acute and chronic respiratory illnesses, 16 (84%) had a moderate risk of bias and two (11%) with a high risk (Supplementary Table 5). Five of nine randomised crossover studies (56%) had a moderate risk of bias, with three (33%) at high risk (Supplementary Table 6). All five non-randomised interventional studies were of moderate-to-high risk of

bias (Supplementary Table 7). For the 19 included observational studies, the overall risk of bias was low-to-moderate (Supplementary Table 8).

Primary outcome

Invasive mechanical ventilation escalation

Need for IMV escalation was reported at variable illness time points (i.e. ranging from within 2 hours to the end of hospital admission) in 29 studies (15 RCTs and 14 observational studies, n = 4778 participants)(6, 8, 28, 30, 31, 34–38, 41–49, 52, 57, 61–63, 66, 67, 71–73) and 6 studies (4 RCTs, 2 observational studies, n = 548 participants)(63, 66, 67, 71–73) for acute and chronic respiratory illnesses respectively (Table 2). Overall need for IMV was defined in this systematic review as any need for IMV escalation, irrespective of the reported time point when IMV was considered.

Table 2
Timepoint at which need for IMV escalation was reported.

Timepoint at which need for IMV escalation was measured	Acute respiratory illnesses 29 studies (15 RCTs, 14 observational studies)	Chronic respiratory illnesses 6 studies (4 RCTs, 2 observational studies)
2 hours	Total: 1 RCT (48)	-
24 hours	Total: 4 studies 3 RCTs (8, 57, 71) 1 Observational study* (62)	Total: 1 RCT (71)
48 hours	Total: 1 RCT (6)	-
72 hours	Total: 4 studies 2 RCTs (36, 44) 2 Observational studies* (45, 62)	
168 hours	Total: 1 Observational study* (45)	-
28 days	Total: 5 studies 3 RCTs (34, 37, 42) 2 Observational studies (30, 47)	-
At the end of hospital stay	Total: 15 studies 5 RCTs (35, 52, 66, 67, 73) 10 Observational studies (28, 31, 38, 41, 43, 46, 49, 61, 63, 72)	Total: 5 studies 3 RCTs (66, 67, 73) 2 Observational studies (63, 72)

*Studies with IMV escalation reported on multiple timepoints: Xing 2021(62): 24 hours, 72 hours, Lee 2019(45): 72 hours, 168 hours. RCT: Randomised controlled trial.

For acute respiratory illnesses, pooled data from 15 RCTs (n = 2239 participants)(6, 8, 34–37, 42, 44, 48, 52, 57, 66, 67, 71, 73) did not demonstrate a significant reduction in *overall need* for IMV escalation for HFNO when compared to COT (RR = 0.82, 95% CI = 0.65–1.05 p = 0.11, I^2 = 23%) (Fig. 2). Similarly, pooled RCT data for IMV escalation at *specified time points* did not reveal any significant reductions for HFNO compared to COT (Supplementary Figs. 6–8).

Secondary analysis of combined data from *all studies* (RCTs and observational studies) demonstrated a significant reduction in need for IMV escalation in favour of HFNO compared to COT *at 24 hours* (RR = 0.32, 95% CI = 0.13–0.79; p = 0.01; 4 studies, n = 487 participants, I^2 = 0%)(8, 57, 62, 71) and *at 28 days*

(RR = 0.84, 95% CI = 0.73–0.96; p = 0.01; 5 studies, n = 1635 participants, I^2 = 35%)(30, 34, 37, 42, 47) (Supplementary Figs. 6–7). However, *overall need* for IMV escalation remained unchanged with secondary analysis (RR = 0.86, 95% CI = 0.73–1.02; p = 0.08; 29 studies, n = 4778 participants, I^2 = 64%)(6, 8, 28, 30, 31, 34–38, 41–49, 52, 57, 61–63, 66, 67, 71–73) (Supplementary Fig. 5a).

For chronic respiratory illnesses, pooled RCT data similarly did not demonstrate a significant reduction in the *overall need* to escalate to IMV for participants receiving HFNO compared to COT (RR = 0.86, 95% CI = 0.33–2.23; p = 0.76; 4 studies, n = 438 participants, I^2 = 0%)(66, 67, 71, 73)(Fig. 2). Only one study on chronic respiratory illness reported need for IMV escalation *at 24 hours* (n = 37 participants)(71) with no between-group difference (HFNO: 5.6%, COT: 5.6%; p = 0.97). Notably, secondary analysis of combined data from *all studies* demonstrated a significant reduction in the overall need for IMV escalation for HFNO compared to COT (RR = 0.68, 95% CI = 0.48–0.97; p = 0.03; 6 studies, n = 548 participants, I^2 = 0%) (63, 66, 67, 71–73) for patients with chronic respiratory illnesses (Supplementary Fig. 5b).

Secondary outcomes

Mortality

Pooled RCT data for acute respiratory illnesses reported no significant difference between *in-hospital mortality* for patients receiving HFNO compared to COT (RR = 1.00, 95% CI 0.85–1.17; p = 1.00; 5 studies, n = 1226 participants, I^2 = 0%)(8, 35, 37, 44, 73) (Fig. 3). Similarly, there were no significant differences in *short-term mortality* at ≤ 30 days (RR = 1.02, 95% CI = 0.85–1.21; p = 0.86; 3 studies, n = 891 participants, I^2 = 0%)(34, 36, 37) and *long-term mortality* at > 30 days (RR = 0.92, 95% CI = 0.65–1.29; p = 0.62; 3 studies, n = 1279 participants, I^2 = 57%)(8, 37, 42) between patients receiving HFNO or COT for acute respiratory illnesses (Supplementary Figs. 10–11). Secondary analysis of pooled data from *all study designs* did not alter any of the mortality outcomes for patients with acute respiratory illnesses (Supplementary Figs. 9a, 10, 11).

For patients with chronic respiratory illnesses, only one RCT reported on *in-hospital mortality* which showed no significant difference between HFNO compared to COT (RR = 0.40, 95% CI = 0.04–4.10; p = 0.44; n = 45 participants)(73) (Fig. 3). No studies reported on *short-term mortality* or *long-term mortality* for chronic respiratory illnesses. Of note, secondary analysis of pooled data from *all study designs* for chronic respiratory illnesses demonstrated a significant reduction of *in-hospital* mortality (RR = 0.58, 95% CI = 0.37–0.92; p = 0.02; 3 studies, n = 155 participants, I^2 = 0%)(64, 74, 75) for participants receiving HFNO compared to COT (Supplementary Fig. 9b).

Non-Invasive Ventilation escalation

Need for NIV escalation was reported in 10 studies(6, 8, 34, 42, 44, 48, 49, 57, 67, 73) for acute respiratory illnesses (9 RCTs)(6, 8, 34, 42, 44, 48, 57, 67, 73) and 2 studies for chronic respiratory illnesses (2 RCTs) (67, 73). Overall need for NIV escalation was pooled from need for NIV escalation measured at different timepoints for individual studies ranging from 24 hours to end of hospital stay.

Pooled RCT data for patients with acute respiratory illnesses revealed a statistically significant reduction in *overall need* for NIV escalation for HFNO compared to COT (RR = 0.62, 95% CI = 0.41–0.94; p = 0.02; 9 studies, n = 1289 participants, I^2 = 40) (Supplementary Fig. 12a). Only one RCT reported on need for NIV escalation at 28 days. Need for NIV escalation at 24 hours was not statistically different compared to COT in patients with acute respiratory illnesses (Supplementary Fig. 13). Secondary analysis of combined data from *all study designs* showed similar results for *overall need* for escalation to NIV, with HFNO significantly reducing NIV escalation need compared to COT (RR = 0.63, 95% CI = 0.43–0.92; p = 0.02; 10 studies, n = 1391 participants, I^2 = 33) in patients with acute respiratory illnesses (Supplementary Fig. 12a).

Pooled RCT data for patients with chronic respiratory illnesses did not reveal any significant differences in *overall need* for NIV escalation between HFNO when compared to COT (RR = 0.96, 95% CI = 0.17–5.26; p = 0.96; 2 studies, n = 365 participants, I^2 = 63) (Supplementary Fig. 12b). No observational or crossover studies reported on need for NIV escalation for patients with chronic respiratory illnesses.

Inpatient admission rates

Of two RCTs examining patients with acute respiratory illnesses within an ED setting, there was no significant risk reduction in the need for inpatient admission for patients receiving HFNO compared to COT (RR = 0.88, 95% CI = 0.53–1.45; p = 0.61; n = 77 participants; I^2 = 4%)(52, 71). However, secondary analysis of pooled data for *all study designs* revealed a small but significant risk reduction in inpatient admission for patients with acute respiratory illnesses receiving HFNO compared to COT (RR = 0.92, 95% CI = 0.85–0.99; p = 0.03; 3 studies, n = 198 participants; I^2 = 0%)(43, 52, 71) (Supplementary Fig. 14).

For patients with chronic respiratory illnesses, hospital admission rates were only reported in one RCT which showed no significant differences between both groups (RR = 1.42, 95% CI = 0.48–4.22; p = 0.53; 1 study, n = 37 participants)(71).

Other hospitalisation-related outcomes

Only one small RCT reported on ICU LOS in patients with chronic respiratory illnesses which showed a significant reduction in favour of HFNO (mean difference= -1.58 days, 95% CI= -2.28 days to -0.88 days; p < 0.001; n = 45 participants)(73). This significant reduction remained with the inclusion of an additional observational study in secondary analysis(72) (Supplementary Fig. 18b).

Meta-analyses of RCTs for all other outcomes, including ICU admission rates, ICU mortality, hospital LOS, and ED LOS, were not significantly different between patients who received either HFNO or COT for both acute and chronic respiratory illnesses. The statistical significance of these outcomes remained unchanged for secondary analysis of combined data from all study designs (Supplementary Figs. 15–19).

Physiological and disability outcomes

Meta-analysis was not performed for change in $PaCO_2$ on arterial blood gases or disability scores (including dyspnoea, comfort, and dryness scores) due to high methodological heterogeneity between studies (Supplementary Tables 11–14). Of the 10 RCTs, 6 (60%) reported no significant difference in change in $PaCO_2$ when comparing HFNO to COT use in patients with acute respiratory illnesses(42, 44, 57, 66, 68, 71) (Supplementary Table 11a). All 4 RCTs that reported a significant difference in change in $PaCO_2$ at one or more timepoints during the study were in favour of HFNO(6, 35, 67, 73). In patients with chronic respiratory illnesses, 3 of 5 RCTs (60%) reported no significant reduction in $PaCO_2$ levels in patients receiving HFNO compared to COT(66, 68, 71) (Supplementary Table 11b). Both RCTs that reported a significant difference in change in $PaCO_2$ at one or more timepoints were in favour of HFNO(67, 73). Secondary analyses of pooled data from *all studies* identified similar findings for patients with acute respiratory illnesses with most studies (20 of 30, 67%) reporting no significant difference in change in $PaCO_2$ levels when comparing HFNO to COT(3, 5, 7, 31, 42–45, 49–51, 54, 56, 57, 60, 61, 65, 66, 68, 71). In contrast, only 4 of the 9 studies (44%) included in secondary analysis for chronic respiratory illnesses found no significant differences in change in PCO_2 between HFNO and COT (65, 66, 68, 71). For *all study designs*, all of the studies which found a significant difference between HFNO and COT (10 studies for acute respiratory illnesses(6, 9, 35, 58, 62, 64, 67, 69, 70, 73), and 5 studies for chronic respiratory illnesses(64, 67, 69, 70, 73)), were in favour of HFNO as well.

Dyspnoea scores were most commonly measured using the Borg scale and visual analogue scale. While half of RCTs (5 of 10, 50%) reported statistically significant lower dyspnoea scores in patients receiving HFNO compared to COT in patients with acute respiratory illnesses(35, 42, 52, 68, 71), both RCTs for chronic respiratory illnesses (2 of 2, 100%) reported significantly lower dyspnoea scores in patients receiving HFNO compared to COT(68, 71). Results from secondary analysis of combined data from *all studies* differed slightly with 12 of 23 (52%) studies(7, 35, 42, 49, 52–55, 58, 64, 68, 71) and 3 of 5 (60%) studies(64, 68, 71) reporting significantly lower dyspnoea scores in patients receiving HFNO compared to COT for acute and chronic respiratory illnesses respectively (Supplementary Tables 12a-b).

Subgroup analyses: Types of respiratory illness

Only secondary analyses of pooled data from RCTs and observational studies were performed for patients with COVID-19 (1 RCT, 4 observational studies), as only one RCT (n = 22 participants) was available (33) reporting ICU LOS. Patients with COVID-19 receiving HFNO compared to COT had significantly reduced short-term mortality at ≤ 30 days (RR = 0.62, 95% CI = 0.48–0.79; 4 observational studies, n = 652 participants; $p < 0.001$; $I^2 = 0\%$)(28, 30–32), long-term mortality at > 30 days (RR = 0.67, 95% CI = 0.48–0.92; 2 observational studies, n = 517 participants; $p = 0.01$; $I^2 = 0\%$)(28, 30), ICU LOS (mean difference=-0.86 days, 95% CI=-1.59 days to -0.13 days; 2 observational studies and 1 RCT study, n = 203 participants; $p = 0.02$; $I^2 = 0\%$)(28, 31, 33), and need for IMV (RR = 0.72, 95% CI = 0.63–0.82; $p < 0.001$; 3 observational studies, n = 560 participants; $I^2 = 0\%$)(28, 30, 31) (Supplementary Figs. 20a-d).

There were no significant differences in outcomes between HFNO and COT in other sub-group analyses by respiratory illness, including COPD exacerbations, asthma exacerbations, and patients with type 2

respiratory failure (Supplementary Figs. 21–23).

Sensitivity analyses: Studies of low risks of bias

Sensitivity analyses were performed excluding studies with an overall high risk of bias, defined as: RCTs and randomised crossover studies with a “high” risk of bias using the ROB2 framework, non-randomised interventional studies with a serious risk of bias using the ROBINS-1 framework, or observational studies with scores < 6 using the Newcastle-Ottawa Scale.

In patients with acute respiratory illnesses, utilising only pooled RCT data from studies not at high risk of bias yielded the same findings for primary and secondary outcomes as reported with all RCTs. Overall need for IMV escalation remained similar for HFNO compared to COT (RR = 0.82, 95% CI = 0.65–1.05; p = 0.11; 14 RCTs, n = 2224 participants; I^2 = 23%)(6, 8, 34, 35, 37, 42, 44, 48, 52, 57, 66, 67, 71, 73).

Interpretation

In this systematic review, HFNO conferred no significant reduction in overall need for IMV escalation or in-hospital mortality when compared to COT for both patients with acute and chronic respiratory illnesses in the primary analyses of RCTs only. However, there was a significant reduction in the overall need for NIV escalation for patients with acute respiratory illnesses compared to COT for patients with acute respiratory illnesses. Additionally, patients with COVID-19 who received HFNO experienced a significant reduction in need for IMV, mortality and ICU LOS, compared to COT.

Acute respiratory illnesses

Recent meta-analyses comparing IMV escalation need in patients with acute respiratory failure have generated mixed results with no significant differences between HFNO and COT in some reviews(10, 25, 26) and significant reductions in IMV escalation for HFNO in others(11, 21, 24). The 2021 European Respiratory Society clinical practice guidelines recommends HFNO over COT in patients with acute hypoxemic respiratory failure, based on pooled data from 12 RCTs and 4 cross-over studies showing a trend but not statistically significant reduction in escalation to IMV with the use of HFNO(26). Our meta-analysis adds to the mixed findings to date, with a reduction in overall IMV requirement that was not statistically significant when considering RCTs only but yielded a statistically significant reduction in IMV escalation at 24 hours and at 28 days when pooling RCTs and observational studies together in patients with acute respiratory illnesses receiving HFNO compared to COT. Furthermore, HFNO significantly reduced need for NIV escalation compared to COT in patients with acute respiratory illnesses. While this inconclusive result may relate to heterogeneity of study populations, methodologies and variation in outcome measurements and timing, there does appear to be a signal that HFNO is superior to COT regarding the need to escalate to IMV, and certain sub-populations of patients with acute respiratory illnesses, such as those with COVID-19, respond better to HFNO than others.

Importantly, similar to previous systematic reviews, we found no significant differences between HFNO and COT in terms of mortality benefit(11, 12, 16, 18–25), ICU admission rates(12), or ICU LOS(11, 17–19, 21, 24, 25) in patients with acute respiratory illnesses. The findings regarding mortality are likely related to the lack of effect of HFNO on overall need to escalate to IMV, as it is well recognised that once someone requires IMV for acute respiratory failure they are at increased risk of dying(38, 74, 75).

This is the first meta-analysis to compare the impacts on mortality and morbidity between HFNO and COT in patients with COVID-19, with substantial outcome benefits identified with HFNO. This evidence supports the increasing adoption globally of HFNO for patients with COVID-19. The pathological processes driving hypoxemia in people with COVID-19 and acute respiratory failure are complex and may involve diffuse interstitial and alveolar oedema, pulmonary endothelial injury, impaired lung diffusion capacity, and pulmonary perfusion abnormalities including impairment of the hypoxic pulmonary vasoconstriction response(76–79). Consequently, large ventilation perfusion mismatches may be seen in acute respiratory failure due to COVID-19 that necessitate higher oxygen flows and fractions of inspired oxygen delivery to the alveoli(76, 78). Compared to COT, HFNO provides higher oxygen flows to match COVID-19 patients increased respiratory flow demands(27). Moreover, HFNO provides greater reduction in inspiratory effort than COT(3, 27), which could reduce the extent of patient self-inflicted lung injury seen in COVID-19 ARF(27, 80). Importantly, with the advent of auto-titration nasal high flow systems that can titrate FiO_2 to oxygen saturation targets(81) and thus reduce the need for healthcare workers to enter patients' rooms to adjust settings, the delivery of HFNO to patients with highly infectious diseases such as COVID-19 may become safer. Notwithstanding the aforementioned, the findings for patients with COVID-19 must be interpretated with caution as pooled data were predominantly from observational studies and therefore subject to the inherent weaknesses of non-interventional studies.

Chronic respiratory illnesses

Although pooled RCT data for chronic respiratory illnesses did not reveal a significant reduction in need for IMV escalation or in-hospital mortality for patients receiving HFNO compared to COT, there was a significant reduction for both of these outcomes, in favour of HFNO, when including both RCTs and observational studies. This was likely due to the fact that 64% of escalations to IMV and 87% of reported in-hospital mortalities occurred in a single small observational study of lung transplant patients with ARF (n = 40 participants)(72). Importantly, findings for chronic respiratory illnesses were not generalisable to sub-populations of restrictive lung diseases like idiopathic pulmonary fibrosis (IPF), albeit patients with those illnesses were under-represented in this study. Nonetheless, a 2019 retrospective study has suggested mortality benefits from HFNO therapy in patients with acute exacerbations of IPF who remain hypoxemic despite COT(82). At the time of writing, no meta-analysis had reported mortality outcomes for HFNO compared to COT in patients with acute exacerbations of COPD, asthma, or interstitial lung disease.

Strengths and limitations

This is the first and largest systematic review to explore the impacts of HFNO compared to COT on morbidity and mortality in patients with a broad range of acute (including COVID-19) and chronic respiratory (including asthma, COPD, and lung cancer) conditions.

Limitations of this review include heterogenous timing of measurements for overall need for IMV escalation as this varied depending on time of treatment failure. Additionally, it is very likely that significant real-world heterogeneity existed between included trials as oxygen therapies were delivered under clinical settings and protocols that varied between studies. Secondly, the overall pooled population was small for certain outcomes, such as hospital admission rates for patients with respiratory illnesses. Thirdly, the risk of bias was moderate for most studies and there was high heterogeneity for some outcomes such as hospital LOS. Thus, large, high-quality RCTs are required to further increase the power of meta-analyses to address several key clinical questions that remain unanswered. Fourthly, it is challenging to blind participants and outcome assessors to the intervention (given the different sensation and delivery devices required for HFNO and COT), thus introducing bias, particularly for more subjective outcomes such as dyspnoea. Importantly, reporting regarding the causes of acute respiratory failure in individual studies was poor, with half of all patients (3035 of 6109, 50%) having no specified acute respiratory illness reported. Therefore, we were unable to further characterise the results by specific causes of ARF, which is crucial for understanding which patient populations with ARF are most likely to benefit from HFNO. It must also be highlighted that some of the meta-analyses were dominated by a few studies, including those performed for hospital mortality and need for IMV escalation, and the weaknesses of these dominant studies should be considered when interpreting the overall pooled results. Lastly, data from patients with a broad spectrum of respiratory conditions were pooled together to reflect real-world hospital setting for generalisability. While this introduces heterogeneity within the study population, it is important to examine HFNO's clinical benefits compared to COT for patients with ARF secondary to heterogenous causes as HFNO becomes more universally adopted.

Conclusion

This systematic review and meta-analysis suggest that HFNO is not superior to COT in reducing need for IMV escalation or in-hospital mortality in patients with heterogeneous acute or chronic respiratory illnesses based on low certainty evidence with high heterogeneity. However, there are therapeutic benefits of HFNO over COT in reducing need for IMV escalation and mortality in patients with COVID-19. Furthermore, HFNO reduced the need for NIV escalation in patients with acute respiratory illnesses. High flow nasal oxygen therapy could therefore be considered for patients with respiratory illnesses who remain hypoxemic despite COT, especially for patients with COVID-19. Future studies should consider comparing health outcomes and cost-effectiveness for HFNO and COT in patients with specific respiratory illnesses and different severities of hypoxemic respiratory failure as therapeutic effects may differ for respiratory illness aetiology and severity. In particular, larger RCTs are required to better delineate key outcomes which play an integral role in formulating clinical guidelines such as mortality,

need for escalation of therapy to IMV and NIV, dyspnoea, patient comfort, ICU length of stay, hospital length of stay, and change in PCO_2 levels.

Points for clinical practice:

1. HFNO and COT are both equally reasonable treatments for patients with undifferentiated acute respiratory illnesses.

2. Early access to HFNO should be considered over COT in patients with acute respiratory failure secondary to COVID-19 infection and, to a lesser extent, in patients with chronic respiratory illnesses.

Questions for future research:

1. Do health outcomes and cost effectiveness for HFNO compared to COT differ for different subgroups of respiratory illnesses?

2. Do health outcomes for HFNO compared to COT differ for varying severities of hypoxemic respiratory failure?

Abbreviations

ARF
Acute respiratory failure
CENTRAL
Cochrane Central Register of Controlled Trials
CI
Confidence interval
COPD
Chronic obstructive pulmonary disease
COT
conventional oxygen therapy
COVID-19
Coronavirus-19
ED
Emergency department
FiO_2
Fraction of inspired oxygen
ICU
Intensive care unit
IMV
Invasive mechanical ventilation
LOS

Length of stay
HFNO
High flow nasal oxygen
NIV
non-invasive mechanical ventilation
$PaCO_2$
partial pressure of carbon dioxide
RCT
Randomised controlled trial
RevMan
Review manager
RR
Risk ratio
ROB
Risk of bias
ROBINS-I
Risk Of Bias In Non-randomised Studies of Interventions
SpO_2
Saturation of peripheral oxygen.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for Publication

Not applicable.

Availability of data and materials

All data analysed during this review can be found in detail within the supplementary materials.

Competing Interests

YK reports in-kind trial support from Air Liquide Healthcare, outside this project. NS reports receiving grant funding from Fisher & Paykel Healthcare for a research study outside this project. The remaining authors have nothing to disclose.

Funding

Not applicable.

Author contributions

Study design was conceived by DS, YK, SK, and NS. DS conducted the literature search and data analysis. All authors (DS,YK,SK,DMS,YN,NS) performed abstract and title screening. DS and SK conducted full-text assessments, with adjudication by YK and NS, and risk of bias assessments with adjudication by YK. DS, YK, and NS drafted the manuscript. NS and YK revised the manuscript for critical intellectual content. All authors read and approved the final manuscript. NS serves as the guarantor for this study and takes responsibility for the content in the manuscript, including data and analysis.

Acknowledgements

Not applicable.

References

1. Frat JP, Coudroy R, Marjanovic N et al. High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure.Annals of Translational Medicine2017; 5(14).
2. Sharma S, Danckers M, Sanghavi D et al.High Flow Nasal Cannula. StatPearls. Treasure Island (FL)2022.
3. Mauri T, Turrini C, Eronia N, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. Am J Respir Crit Care Med. 2017;195(9):1207–15.
4. Pacheco E, Wawrzeniak IC, Victorino JA et al. Physiological effects of high flow nasal therapy in patients with acute respiratory failure measured by esophageal catheter and electrical impedance tomography: A pilot study. *American Journal of Respiratory and Critical Care Medicine. Conference* 2019; 199(9).
5. Delorme M, Bouchard PA, Simon M, et al. Effects of high-flow nasal cannula on the work of breathing in patients recovering from acute respiratory failure. Crit Care Med. 2017;45(12):1981–8.
6. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus venturi mask oxygen therapy after extubation: Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med. 2014;190(3):282–8.
7. Lenglet H, Sztrymf B, Leroy C, et al. Humidified high flow nasal oxygen during respiratory failure in the emergency department: Feasibility and efficacy. Respir Care. 2012;57(11):1873–8.
8. Jones PG, Kamona S, Doran O, et al. Randomized controlled trial of humidified high-flow nasal oxygen for acute respiratory distress in the emergency department: The HOT-ER study. Respir Care. 2016;61(3):291–9.
9. Sztrymf B, Messika J, Mayot T, et al. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: A prospective observational study. J Crit Care. 2012;27(3):e9–324.

10. Baldomero AK, Melzer AC, Greer N, et al. Effectiveness and Harms of High-Flow Nasal Oxygen for Acute Respiratory Failure: An Evidence Report for a Clinical Guideline from the American College of Physicians. Ann Intern Med. 2021;174(7):952–66.
11. Ferreyro BL, Angriman F, Munshi L, et al. Association of Noninvasive Oxygenation Strategies with All-Cause Mortality in Adults with Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis. JAMA - Journal of the American Medical Association. 2020;324(1):57–67.
12. Huang CC, Lan HM, Li CJ, et al. Use High-Flow Nasal Cannula for Acute Respiratory Failure Patients in the Emergency Department: A Meta-Analysis Study. Emergency Medicine International; 2019.
13. Lee CC, Mankodi D, Shaharyar S, et al. High flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation in adults with acute hypoxemic respiratory failure: A systematic review. Respir Med. 2016;121:100–8.
14. Maitra S, Som A, Bhattacharjee S, et al. Comparison of high-flow nasal oxygen therapy with conventional oxygen therapy and noninvasive ventilation in adult patients with acute hypoxemic respiratory failure: A meta-analysis and systematic review. J Crit Care. 2016;35:138–44.
15. Monro-Somerville T, Sim M, Ruddy J, et al. The Effect of High-Flow Nasal Cannula Oxygen Therapy on Mortality and Intubation Rate in Acute Respiratory Failure: A Systematic Review and Meta-Analysis. Crit Care Med. 2017;45(4):e449–56.
16. Nedel WL, Deutschendorf C, Moraes RF, et al. High-Flow Nasal Cannula in Critically Ill Subjects with or at Risk for Respiratory Failure: A Systematic Review and Meta-Analysis. Respir Care. 2017;62(1):123–32.
17. Ni YN, Luo J, Yu H, et al. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. Am J Emerg Med. 2018;36(2):226–33.
18. Ni YN, Luo J, Yu H, et al. Can High-flow Nasal Cannula Reduce the Rate of Endotracheal Intubation in Adult Patients with Acute Respiratory Failure Compared with Conventional Oxygen Therapy and Noninvasive Positive Pressure Ventilation?: A Systematic Review and Meta-analysis. Chest. 2017;151(4):764–75.
19. Rochwerg B, Granton D, Wang DX, et al. High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis. Intensive Care Med. 2019;45(5):563–72.
20. Sklar MC, Mohammed A, Orchanian-Cheff A, et al. The Impact of High-Flow Nasal Oxygen in the Immunocompromised Critically Ill: A Systematic Review and Meta-Analysis. Respir Care. 2018;63(12):1555–66.
21. Wang Y, Ni Y, Sun J, Liang Z. Use of High-Flow Nasal Cannula for Immunocompromise and Acute Respiratory Failure: A Systematic Review and Meta-Analysis. J Emerg Med. 2020;58(3):413–23.
22. Zayed Y, Banifadel M, Barbarawi M, et al. Noninvasive Oxygenation Strategies in Immunocompromised Patients with Acute Hypoxemic Respiratory Failure: A Pairwise and Network

Meta-Analysis of Randomized Controlled Trials. J Intensive Care Med. 2020;35(11):1216–25.
23. Zayed Y, Barbarawi M, Kheiri B, et al. Initial noninvasive oxygenation strategies in subjects with de novo acute hypoxemic respiratory failure. Respir Care. 2019;64(11):1433–44.
24. Lewis SR, Baker PE, Parker R, et al. High-flow nasal cannulae for respiratory support in adult intensive care patients. Cochrane Database Syst Rev. 2021;3(3):CD010172.
25. Liang S, Liu Z, Qin Y et al. The effect of high flow nasal oxygen therapy in intensive care units: a systematic review and meta-analysis.Expert Rev Respir Med2021:1–11.
26. Oczkowski S, Ergan B, Bos L, et al. ERS Clinical Practice Guidelines: High-flow nasal cannula in acute respiratory failure. Eur Respir J. 2022;59(4):2101574.
27. Crimi C, Pierucci P, Renda T et al. High-Flow Nasal Cannula and COVID-19: A Clinical Review.Respir Care2021.
28. Bonnet N, Martin O, Boubaya M et al. High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: a retrospective study.Annals of Intensive Care2021; 11(1).
29. Delbove A, Foubert A, Mateos F et al. High flow nasal cannula oxygenation in COVID-19 related acute respiratory distress syndrome: a safe way to avoid endotracheal intubation?Therapeutic Advances in Respiratory Disease2021;15.
30. Demoule A, Baron A, Darmon M, et al. High-flow nasal cannula in critically Ill patients with severe COVID-19. Am J Respir Crit Care Med. 2020;202(7):1039–42.
31. Sayan I, Altinay M, Cinar AS, et al. Impact of HFNC application on mortality and intensive care length of stay in acute respiratory failure secondary to COVID-19 pneumonia. Heart Lung. 2021;50(3):425–9.
32. Stempek S, Hansen C, Liesching T, et al. Outcomes of patients with COVID-19-associated ards treated with hfnc vs. conventional oxygen therapy. Crit Care Med. 2021;49(1 SUPPL 1):122.
33. Teng XB, Shen Y, Han MF et al. The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia.European Journal of Clinical Investigation2021; 51(3).
34. Alptekinoglu N, Temel S, Yuksel R, et al. The Use of High-Flow Nasal Oxygen Vs. Standard Oxygen Therapy in Hematological Malignancy Patients with Acute Respiratory Failure in Hematology Wards. Turk J Med Sci. 2021;01:01.
35. Andino R, Vega G, Pacheco S et al. High-flow nasal oxygen reduces endotracheal intubation: a randomized clinical trial.Therapeutic Advances in Respiratory Disease2020;14.
36. Arman PD, Varn MN, Povian S et al. Effects of direct extubation to high-flow nasal cannula compared to standard nasal cannula in patients in the intensive care unit.American journal of respiratory and critical care medicine2017;195.
37. Azoulay E, Lemiale V, Mokart D, et al. Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients with Acute Respiratory Failure: The HIGH Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2018;320(20):2099–107.

38. Azoulay E, Pickkers P, Soares M, et al. Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study. Intensive Care Med. 2017;43(12):1808–19.
39. Cuquemelle E, Pham T, Papon JF, et al. Heated and humidified high-flow oxygen therapy reduces discomfort during hypoxemic respiratory failure. Respir Care. 2012;57(10):1571–7.
40. Dumas G, Chevret S, Lemiale V, et al. Oxygenation/non-invasive ventilation strategy and risk for intubation in immunocompromised patients with hypoxemic acute respiratory failure. Oncotarget. 2018;9(72):33682–93.
41. Ellison A, Ingley S, Pugh R. Nasal high flow oxygen for community-acquired pneumonia. J Intensive Care Soc. 2016;17(4 Supplement 1):108–9.
42. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185–96.
43. Gedikloglu M, Gulen M, Satar S et al. How to treat patients with acute respiratory failure? Conventional oxygen therapy versus high-flow nasal cannula in the emergency department.Hong Kong Journal of Emergency Medicine2019.
44. Hu TY, Lee CH, Cheng KH, et al. Effect of high-flow nasal oxygen vs. Conventional oxygen therapy on extubation outcomes and physiologic changes for patients with high risk of extubation failure in the medical ICU: A tertiary center, randomized, controlled trial. Int J Gerontol. 2020;14(1):36–41.
45. Lee M, Kim JH, Jeong IB, et al. Protecting Postextubation Respiratory Failure and Reintubation by High-Flow Nasal Cannula Compared to Low-Flow Oxygen System: Single Center Retrospective Study and Literature Review. Acute Crit. 2019;34(1):60–70.
46. Lemiale V, De Jong A, Dumas G, et al. Oxygenation Strategy During Acute Respiratory Failure in Critically Ill Immunocompromised Patients. Crit Care Med. 2020;48(9):e768–75.
47. Lemiale V, Resche-Rigon M, Mokart D, et al. High-Flow Nasal Cannula Oxygenation in Immunocompromised Patients with Acute Hypoxemic Respiratory Failure: A Groupe de Recherche Respiratoire en Reanimation Onco-Hematologique Study. Crit Care Med. 2017;45(3):e274–80.
48. Lemiale V, Mokart D, Mayaux J et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: A multicenter randomized trial.Critical Care2015; 19(1).
49. Mace J, Marjanovic N, Faranpour F, et al. Early high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure in the ED: A before-after study. Am J Emerg Med. 2019;37(11):2091–6.
50. Mauri T, Alban L, Turrini C, et al. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. Intensive Care Med. 2017;43(10):1453–63.
51. Peters SG, Holets SR, Gay PC. High-flow nasal cannula therapy in do-not-intubate patients with hypoxemic respiratory distress. Respir Care. 2013;58(4):597–600.
52. Rittayamai N, Tscheikuna J, Praphruetkit N, et al. Use of High-Flow Nasal Cannula for Acute Dyspnea and Hypoxemia in the Emergency Department. Respir Care. 2015;60(10):1377–82.

53. Rittayamai N, Tscheikuna J, Rujiwit P. High-flow nasal cannula versus conventional oxygen therapy after endotracheal extubation: A randomized crossover physiologic study. Respir Care. 2014;59(4):485–90.
54. Roca O, Riera J, Torres F, et al. High-flow oxygen therapy in acute respiratory failure. Respir Care. 2010;55(4):408–13.
55. Ruangsomboon O, Dorongthom T, Chakorn T, et al. High-Flow Nasal Cannula Versus Conventional Oxygen Therapy in Relieving Dyspnea in Emergency Palliative Patients With Do-Not-Intubate Status: A Randomized Crossover Study. Ann Emerg Med. 2019;75(5):615–26.
56. Schwabbauer N, Berg B, Blumenstock G et al. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: Effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV).BMC Anesthesiology2014; 14(1).
57. Song HZ, Gu JX, Xiu HQ, et al. The value of high-flow nasal cannula oxygen therapy after extubation in patients with acute respiratory failure. Clin (Sao Paulo Brazil). 2017;72(9):562–7.
58. Song Y, Zhang J, Xing J et al. Comparison of high-flow nasal oxygen cannula therapy versus a standard oxygen face mask in patients with hypostatic pneumonia.Journal of International Medical Research2021; 49(6).
59. Spoletini G, Mega C, Pisani L, et al. High-flow nasal therapy vs standard oxygen during breaks off noninvasive ventilation for acute respiratory failure: A pilot randomized controlled trial. J Crit Care. 2018;48:418–25.
60. Vargas F, Saint-Leger M, Boyer A, et al. Physiologic effects of high-flow nasal Cannula oxygen in critical care subjects. Respir Care. 2015;60(10):1369–76.
61. Xia M, Li W, Yao J, et al. A postoperative comparison of high-flow nasal cannula therapy and conventional oxygen therapy for esophageal cancer patients. Annals of palliative medicine. 2021;10(3):2530–9.
62. Xing D, Chen YH, Wang LT et al. Evaluation of the therapeutic effect of high-flow nasal cannula oxygen therapy on patients with aspiration pneumonia accompanied by respiratory failure in the post-stroke sequelae stage.BMC Pulmonary Medicine2021; 21(1).
63. Branick K, Jackson JA, McCann D et al. Use of nasal high flow oxygen on the general medical floor can prevent ICU admission and escalation of care in COPD patients. *American Journal of Respiratory and Critical Care Medicine. Conference* 2019; 199(9).
64. Crimi C, Noto A, Cortegiani A, et al. High Flow Nasal Therapy Use in Patients with Acute Exacerbation of COPD and Bronchiectasis: A Feasibility Study. COPD: J Chronic Obstr Pulmonary Disease. 2020;17(2):184–90.
65. Di Mussi R, Spadaro S, Stripoli T, et al. High-flow nasal cannula oxygen therapy decreases postextubation neuroventilatory drive and work of breathing in patients with chronic obstructive pulmonary disease. Crit Care (London England). 2018;22(1):180.
66. Geng W, Batu W, You S et al. High-Flow Nasal Cannula: A Promising Oxygen Therapy for Patients with Severe Bronchial Asthma Complicated with Respiratory Failure.Canadian Respiratory

Journal2020.

67. Li XY, Tang X, Wang R, et al. High-flow nasal cannula for chronic obstructive pulmonary disease with acute compensated hypercapnic respiratory failure: A randomized, controlled trial. Int J COPD. 2020;15:3051–61.
68. Raeisi S, Fakharian A, Ghorbani F, et al. Value and safety of high flow oxygenation in the treatment of inpatient asthma: A Randomized, Double-blind, Pilot Study. Iran J Allergy Asthma Immunol. 2019;18(6):615–23.
69. Piquilloud L, Beloncle F, Olivier PY et al. Nasal high flow oxygen can be used in hypercapnic respiratory failure due to COPD exacerbation without increase in PaCO2. *Annals of Intensive Care. Conference: French Intensive Care Society International Congress.* 2020; 10(Supplement 1).
70. Pilcher J, Eastlake L, Richards M, et al. Physiological effects of titrated oxygen via nasal high-flow cannulae in COPD exacerbations: A randomized controlled cross-over trial. Respirology. 2017;22(6):1149–55.
71. Ruangsomboon O, Limsuwat C, Praphruetkit N, et al. Nasal High-flow Oxygen Versus Conventional Oxygen Therapy for Acute Severe Asthma Patients: A Pilot Randomized Controlled Trial. Acad Emerg Med. 2021;28(5):530–41.
72. Roca O, De Acilu MG, Caralt B, et al. Humidified high flow nasal cannula supportive therapy improves outcomes in lung transplant recipients readmitted to the intensive care unit because of acute respiratory failure. Transplantation. 2015;99(5):1092–8.
73. Saeed A, Wagih K, Hussein N. Evaluation of nasal optiflow device in management of COPD patients in acute exacerbations. *European Respiratory Journal. Conference: European Respiratory Society Annual Congress* 2015; 46(suppl. 59).
74. Patel U, Malik P, Usman MS, et al. Age-Adjusted Risk Factors Associated with Mortality and Mechanical Ventilation Utilization Amongst COVID-19 Hospitalizations-a Systematic Review and Meta-Analysis. SN Compr Clin Med. 2020;2(10):1740–9.
75. Stauffer JL, Fayter NA, Graves B, et al. Survival following mechanical ventilation for acute respiratory failure in adult men. Chest. 1993;104(4):1222–9.
76. Allado E, Poussel M, Valentin S, et al. The Fundamentals of Respiratory Physiology to Manage the COVID-19 Pandemic: An Overview. Front Physiol. 2020;11:615690.
77. Dhont S, Derom E, Van Braeckel E, et al. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res. 2020;21(1):198.
78. Santamarina MG, Boisier D, Contreras R, et al. COVID-19: a hypothesis regarding the ventilation-perfusion mismatch. Crit Care. 2020;24(1):395.
79. Gattinoni L, Gattarello S, Steinberg I et al. COVID-19 pneumonia: pathophysiology and management.Eur Respir Rev2021; 30(162).
80. Weaver L, Das A, Saffaran S, et al. High risk of patient self-inflicted lung injury in COVID-19 with frequently encountered spontaneous breathing patterns: a computational modelling study. Ann Intensive Care. 2021;11(1):109.

81. Harper J, Kearns N, Bird G et al. Automatic versus manual oxygen titration using a novel nasal high-flow device in medical inpatients with an acute illness: a randomised controlled trial.BMJ Open Respir Res2021; 8(1).
82. Vianello A, Arcaro G, Molena B, et al. High-flow nasal cannula oxygen therapy to treat acute respiratory failure in patients with acute exacerbation of idiopathic pulmonary fibrosis. Ther Adv Respir Dis. 2019;13:1753466619847130.

Figures

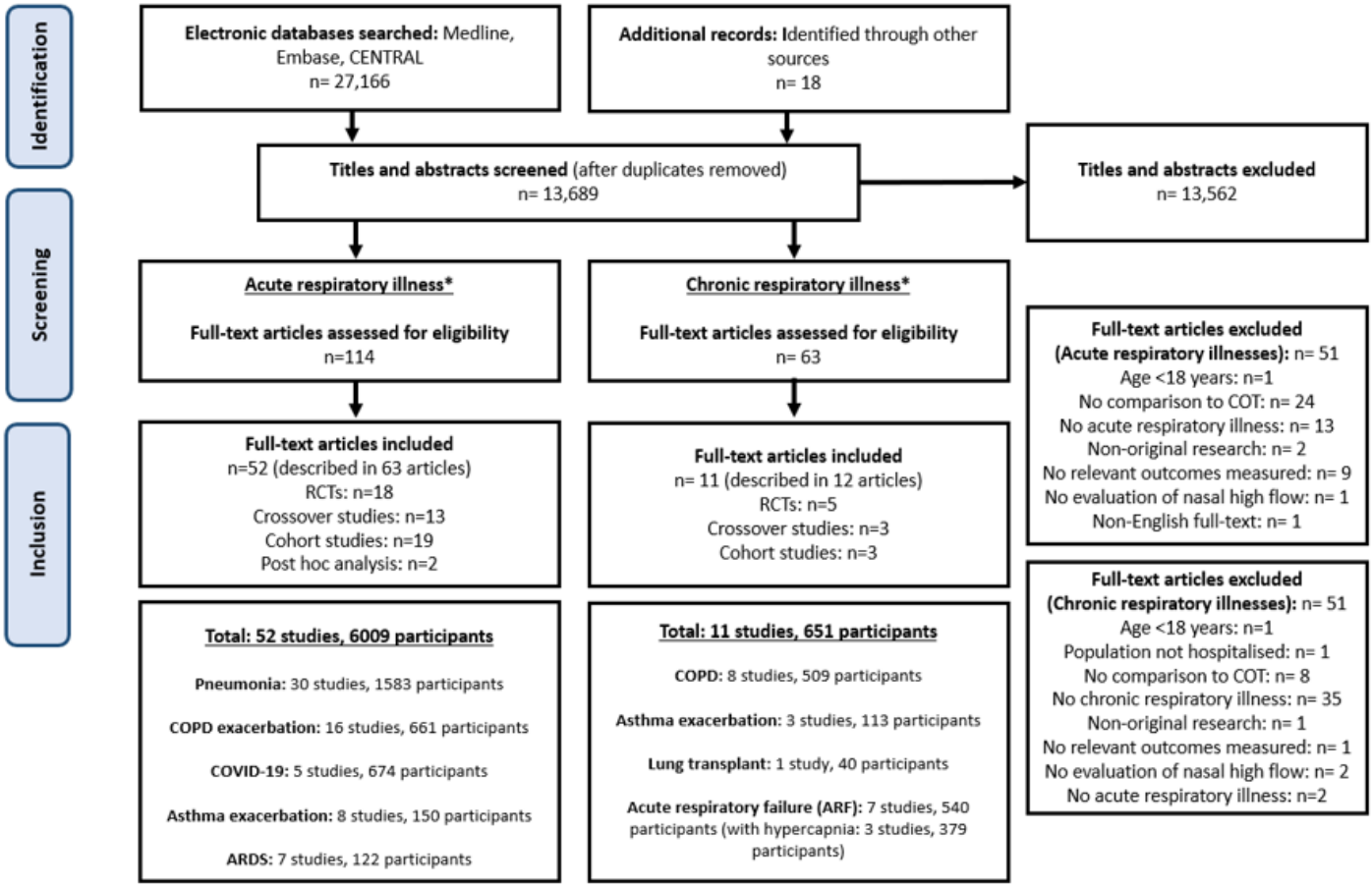

Figure 1

PRISMA Flow Chart and types of respiratory illnesses. *All studies for chronic respiratory illnesses studies were included in the studies for acute respiratory illnesses. ARDS: Acute respiratory distress syndrome. CENTRAL: Cochrane Central Register of Controlled Trials. COPD: Chronic obstructive pulmonary disease, COVID-19: Coronavirus-19.

Figure 2a: *Acute respiratory illnesses- RCTs: need for IMV escalation*

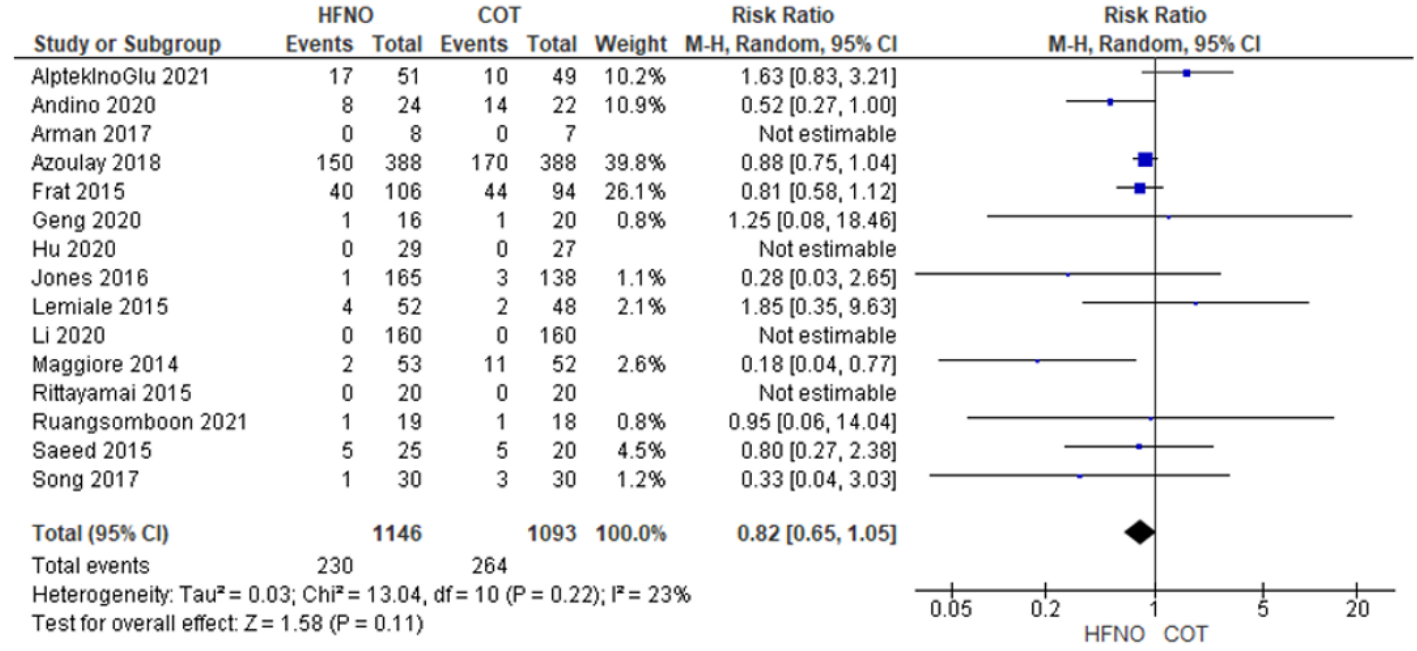

Figure 2b: *Chronic respiratory illnesses- RCTs: need for IMV escalation*

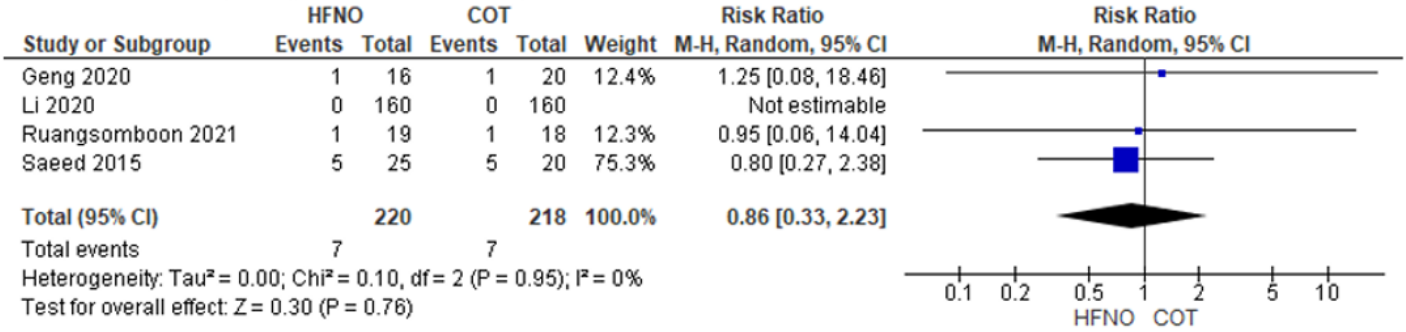

Figure 2

Invasive mechanical ventilation in patients with acute respiratory illnesses and chronic respiratory illnesses. For patients with acute respiratory illnesses, timing of escalation to IMV were as follows: IMV at 2 hours:(48) IMV at 24 hours:(8, 57, 71) IMV at 48 hours:(6) IMV at 72 hours:(36, 44) IMV at 28 days:(34, 37, 42). IMV: Invasive mechanical ventilation. HFNO: High flow nasal oxygen. COT: Conventional oxygen therapy.

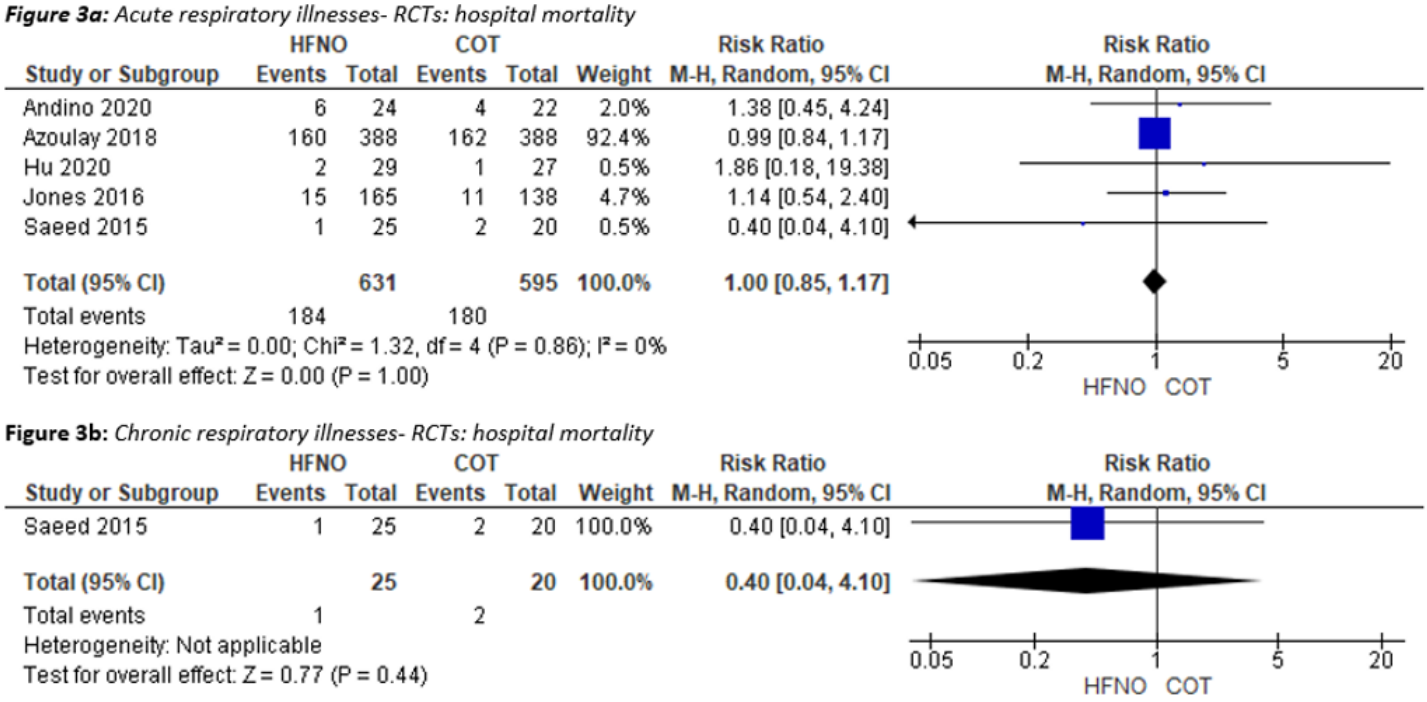

Figure 3

Hospital mortality in patients with acute respiratory illnesses and chronic respiratory illnesses. HFNO: High flow nasal oxygen. COT: Conventional oxygen therapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- HFNOvsCOTSupplementarymaterials160123.pdf