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SYSTEMATIC REVIEW

High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: a systematic review and meta-analysis

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Abstract

Background: This systematic review and meta-analysis summarizes the safety and efficacy of high flow nasal cannula (HFNC) in patients with acute hypoxemic respiratory failure.

Methods: We performed a comprehensive search of MEDLINE, EMBASE, and Web of Science. We identified randomized controlled trials that compared HFNC to conventional oxygen therapy. We pooled data and report summary estimates of effect using relative risk for dichotomous outcomes and mean difference or standardized mean difference for continuous outcomes, with 95% confidence intervals. We assessed risk of bias of included studies using the Cochrane tool and certainty in pooled effect estimates using GRADE methods.

Results: We included 9 RCTs ($n = 2093$ patients). We found no difference in mortality in patients treated with HFNC (relative risk [RR] 0.94, 95% confidence interval [CI] 0.67–1.31, moderate certainty) compared to conventional oxygen therapy. We found a decreased risk of requiring intubation (RR 0.85, 95% CI 0.74–0.99) or escalation of oxygen therapy (defined as crossover to HFNC in the control group, or initiation of non-invasive ventilation or invasive mechanical ventilation in either group) favouring HFNC-treated patients (RR 0.71, 95% CI 0.51–0.98), although certainty in both outcomes was low due to imprecision and issues related to risk of bias. HFNC had no effect on intensive care unit length of stay (mean difference [MD] 1.38 days more, 95% CI 0.90 days fewer to 3.66 days more, low certainty), hospital length of stay (MD 0.85 days fewer, 95% CI 2.07 days fewer to 0.37 days more, moderate certainty), patient reported comfort (SMD 0.12 lower, 95% CI 0.61 lower to 0.37 higher, very low certainty) or patient reported dyspnea (standardized mean difference [SMD] 0.16 lower, 95% CI 1.10 lower to 1.42 higher, low certainty). Complications of treatment were variably reported amongst included studies, but little harm was associated with HFNC use.

Conclusion: In patients with acute hypoxemic respiratory failure, HFNC may decrease the need for tracheal intubation without impacting mortality.

Keywords: Respiratory failure, High flow nasal cannula, Meta-analysis

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Introduction

Acute hypoxemic respiratory failure can result from a myriad of acute etiologies such as pneumonia or the acute respiratory distress syndrome or from exacerbation of underlying heart or lung disease. Patients presenting with hypoxia are treated with high concentrations of inhaled oxygen. This therapy may be delivered conventionally using a number of different interfaces including nasal prongs, facemask with reservoir or Venturi mask. For those with severe hypoxia, escalation of treatment to invasive positive pressure ventilation may be necessary.

Given the risks associated with intubation and the use of invasive ventilation, a number of studies have investigated the role of non-invasive ventilation (NIV) in patients with acute respiratory failure [1–4]. Although NIV use in this setting may decrease the need for intubation as compared to conventional oxygen therapy, certainty in these conclusions is limited by imprecision [5, 6]. NIV use is also associated with development of complications including increased risk of aspiration, facial skin breakdown, an inability to control respiratory drive leading to excessively high tidal volumes and patient discomfort related to inability to communicate and eat during therapy [7]. Due to these limitations, the 2017 European Respiratory Society/American Thoracic Society NIV clinical practice guideline made no recommendation regarding the use of NIV for acute de novo respiratory failure [8].

High flow nasal cannula (HFNC) is a non-invasive, high concentration oxygen delivery interface that circumvents some of the limitations of conventional NIV. Although historically used in neonates, HFNC use has been increasing over the last number of years in critically ill adults. The single inspiratory limb of HFNC allows for airflows as high as 50–60 litres/minute to achieve inspired oxygen fractions (FiO2) as high as 95–100%. Higher flows allow clinicians to better match the inspiratory demands of patients who are in acute hypoxemic respiratory failure. As application of HFNC in adult ICUs is relatively recent, the evidence supporting its use remains limited and is composed of predominantly observational studies [9]. Previous systematic reviews have identified only a small number of randomized controlled trials (RCTs) examining the role of HFNC in the setting of acute hypoxemic respiratory failure, and the total number of participants is under 1000 across all available studies [9–13]. Previous systematic reviews were also limited by imprecision (given the small numbers), combining of observational and RCT data [9], and pooling across heterogeneous patient populations (including patients with acute respiratory failure and those in the postoperative setting or post-extubation) [9, 12, 13].

Take-home message

This meta-analysis of RCT data suggests in patients with acute hypoxemic respiratory failure, HFNC may decrease the need for intubation without impacting mortality.

The recently published HIGH study randomized 776 immuno-compromised critically ill adults with acute hypoxemic respiratory failure to either HFNC or conventional oxygen therapy [14]. This study almost doubles the data available for examining the role of HFNC in this setting. We sought to perform a systematic review and meta-analysis, including recent data, examining the role of HFNC in critically ill adults with hypoxemic respiratory failure.

Methods

The protocol for this systematic review was registered on PROSPERO (CRD42018114132). This systematic review and meta-analysis was performed to support a planned clinical practice guideline addressing the role of HFNC in patients with acute hypoxemic respiratory failure. The manuscript and study have been endorsed by the European Society of Intensive Care Medicine (ESICM).

Data sources and searches

We performed a comprehensive search of MEDLINE, EMBASE, and Web of Science for randomized controlled trials published from January 1st 2007 through October 25, 2018. HFNC was not widely used in adults prior to 2007. We searched for studies that referred to adults treated with HFNC using the key words "humans" together with "adult", "mature" or "grown" and key words "high flow nasal cannula", "high flow nasal therapy", "high flow nasal oxygen", "high flow oxygen therapy", "high flow therapy", "optiflow (respiration)" or "nasal highflow". We did not apply any language or quality restrictions.

Study selection

We screened all citations in duplicate with disagreements resolved by discussion and third party adjudication, as required. Reviewers (DW, DG) worked in pairs to screen all potentially relevant citations and references in two stages, initially assessing titles and abstracts, and then full manuscripts for those that were possibly eligible. We captured reasons for exclusion at the full manuscript review stage.

We included all RCTs comparing the use of HFNC with conventional oxygen therapy in critically ill patients with acute hypoxemic respiratory failure of any cause. We excluded case reports, case series, observational studies and studies that used NIV or invasive mechanical

ventilation as the only comparator. We excluded studies that investigated the role of HFNC before tracheal intubation or for post-extubation respiratory support. Although we had initially intended to capture studies that used NIV as the only comparator to HFNC, we subsequently decided to exclude these studies in order to limit clinical heterogeneity. We included the following outcomes: mortality (if multiple time points reported, we used longest available), need for intubation, ICU and hospital lengths of stay, treatment failure (defined as crossover to HFNC in the control group, or initiation of non-invasive ventilation or invasive mechanical ventilation in either group), patient comfort (as reported by the individual study authors), dyspnea, and complications of therapy. If multiple time points for comfort or dyspnea were reported, we used the first recorded after randomization.

Data extraction and quality assessment

Two reviewers (DG, DW) performed data extraction independently and in duplicate using predefined data abstraction forms. A third reviewer (BR) resolved disagreements. Abstracted data included study characteristics, demographic data, intervention and control details, outcome data, and individual study risk of bias. For the purposes of this review, escalation of therapy was defined as an increase in oxygen support therapy, either to HFNC (if in the control group), NIV or invasive mechanical ventilation.

We assessed Risk of Bias (RoB) independently and in duplicate, for each outcome of individual studies using a modified Cochrane RoB tool [15] that classifies RoB as "low", "probably low", "probably high", or "high" for each of the following domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting and other bias. We rated the overall RoB as the highest risk attributed to any criterion. We assessed the overall certainty of evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [16]. Disagreements regarding RoB and GRADE assessments were resolved by discussion.

Data analysis

We used DerSimonian and Laird random effects models to conduct the meta-analyses. All analyses were performed in RevMan 5.3 (Cochrane Collaboration, Oxford) software. Study weights were generated using the inverse variance method. We present results as relative risks (RRs) for dichotomous outcomes and as mean differences (MDs) for continuous outcomes, both with 95% confidence intervals (CIs). For continuous outcomes, we assumed a normal distribution (i.e. median = mean) and converted inter-quartile ranges to standard deviation using methods suggested by the Cochrane Collaboration [17]. Where continuous outcomes were reported graphically only, we used an online plot digitlizer to provide numeric estimates for analyses (plotdigitizer.sourceforge.net).

We assessed for heterogeneity between studies using the χ^2 test for homogeneity, the I^2 statistic [18], and visual inspection of the forest plots. We considered the magnitude and direction of heterogeneity when considering whether to rate down our certainty in the evidence for inconsistency. We considered a number of a priori subgroup analyses: hypoxemic and hypercarbic respiratory failure versus hypoxemic respiratory failure alone, hypothesizing that HFNC would be more beneficial in hypoxemic respiratory failure alone; pulmonary edema versus other causes of respiratory failure, hypothesizing that HFNC would be more beneficial in pulmonary edema; immunocompromised versus other populations with respiratory failure, hypothesizing that HFNC would be more beneficial in the immunocompromised; severe hypoxia (PaO2:FiO2 ratio $\leq$ 150) versus mild-moderate hypoxia (PaO2:FiO2 ratio > 150), hypothesizing that HFNC would be more beneficial in those with mild-moderate hypoxia; those with bilateral pulmonary infiltrates versus those without bilateral pulmonary infiltrates, hypothesizing that HFNC would be more beneficial in those without bilateral infiltrates; and high risk of bias studies versus low risk of bias studies, hypothesizing that HFNC would be more beneficial in high risk of bias studies. However, due to a low number of included trials, low number of events and overall lack of sufficient data, we did not perform this analysis as any results would be too susceptible to imprecision and meaningful conclusions would not be possible. The only subgroup analysis that was possible was one comparing high risk of bias versus low risk of bias studies. We also performed one post hoc subgroup analysis comparing patients admitted to the emergency department versus those admitted to the intensive care unit with acute hypoxemic respiratory failure, hypothesizing that HFNC would be more beneficial in those admitted to the emergency department. At the request of peer reviewers, we performed two post hoc sensitivity analyses, one excluding a trial of emergency department patients who were thought to be less hypoxemic [19], and one with a short followup end-point [20].

We conducted trial sequential analysis (TSA) [21] using a random effects model for the mortality and the invasive mechanical ventilation outcomes. For the TSA, we used a statistical significance level of 5%, a power of 80%, and a relative risk reduction of 15%. We used a model variance based heterogeneity correction. TSA was performed using Trial Sequential Analysis v.0.9.5.10 beta

(Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, www.ctu.dk/tsa).

Results

Search results and study characteristics

Of the 446 citations identified in our search, we retrieved 169 full texts and included 9 RCTs that proved eligible [19, 20, 22–28] (Fig. 1). Supplementary Table 1 presents the details of the eligible trials. The trials randomized between 14 and 776 patients, and one of them used a crossover design [28]. Five trials were performed in the ICU setting [20, 22, 24, 26, 28], while four trials were conducted in the emergency department [19, 23, 25, 27]. One trial included only patients with cardiogenic pulmonary edema [19], while two trials included only patients with an immunocompromised state [14, 20]. Criteria for hypoxemia varied amongst the included trials, with some using SpO2 cutoffs (most commonly < 90–95%) [19, 20, 22, 23, 25, 27], PaO2 cutoffs (< 55–60 mmHg) [22, 28], PF ratio (< 300) cutoffs [24] or some using a combination of these parameters in addition to an elevated respiratory rate (most commonly > 22–25/min) [19, 23–27]. All included studies initiated flows at 35 litres/minute or over in the HFNC group. One of the included trials included a third arm that received NIV, however data from this intervention were not included in the analysis [24].

Table 1 presents individual study risk of bias. None of the included trials were blinded. Other than this domain, five of the studies were at low or probably low risk of bias [19, 22, 24, 26, 28] while three trials had incomplete data [23, 25, 27], and one trial had selective reporting [20].

Outcomes

Table 2 shows the summary of findings for all outcomes including the certainty of evidence and reasons for rating down the evidence. Although HFNC had no effect on mortality (relative risk [RR] 0.94, 95% CI 0.67–1.31, 1.6% absolute risk reduction, 95% CI 8.4% reduction to 9.0% increase, moderate certainty) compared to conventional oxygen therapy (Fig. 2), HFNC therapy may reduce the need for invasive mechanical ventilation as compared to conventional oxygen therapy (RR 0.85, 95% CI 0.74–0.99, 4.4% absolute risk reduction, 95% CI 0.3% reduction to 7.6% reduction, low certainty) with an NNT of 23 (95% CI 13–333) (Fig. 3). The TSA showed the required information size was not met for either of these outcomes (Supplementary Fig. 1 and 2). There was no credible subgroup effect on this outcome based on individual study risk of bias (Fig. 3).

Similarly, HFNC may reduce the need for escalation of therapy (RR 0.71, 95% CI 0.51–0.98, 9.3% absolute

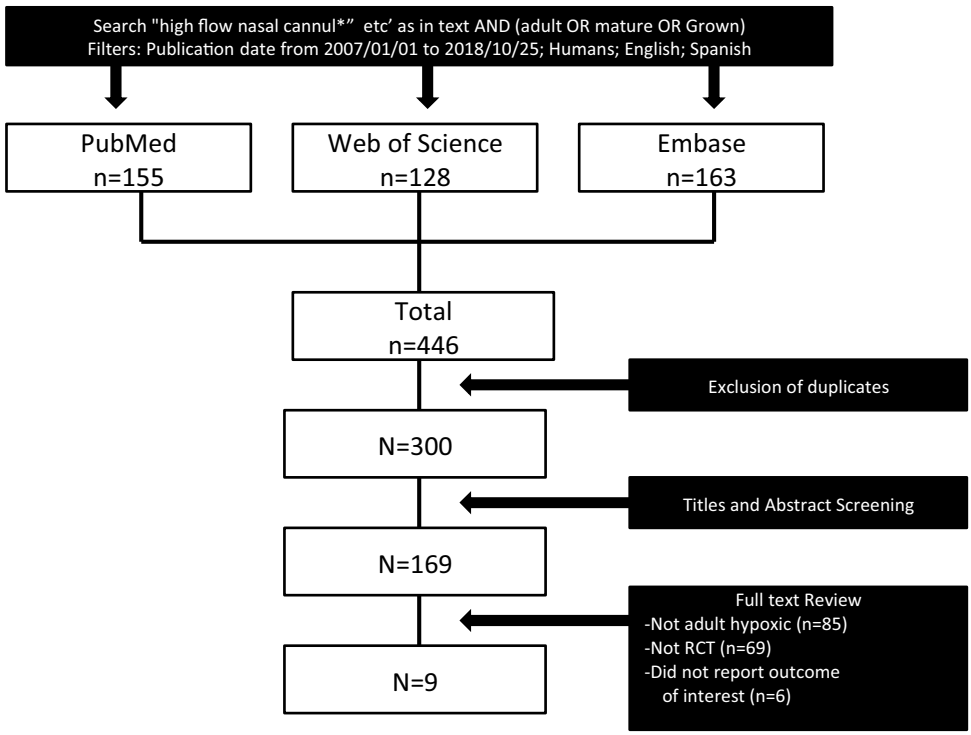

Fig. 1 PRISMA flow—study inclusion

Table 1 Individual study risk of bias

Study (author, years)	Randomization generation	Allocation concealment	Blinding	Incomplete data	Selective reporting	Other	Overall ROB
Azoulay et al. [14]	Low	Low	High	Low	Low	Low	Low
Bell et al. [23]	Low	Low	High	High	Low	Low	High
Doshi [29]	Low	Low	High	Low	Low	Low	Low
Frat et al. [24]	Low	Low	High	Low	Low	Low	Low
Jones et al. [25]	Low	Low	High	High	Low	Low	High
Lemiale et al. [20]	Probably low	Low	High	Low	Probably high	Low	High
Makdee et al. [19]	Probably low	Low	High	Low	Low	Probably low	Low
Parke et al. [26]	Low	Low	High	Probably low	Probably low	Low	Low
Rittayamalet al. [27]	Probably low	Low	High	High	Probably low	Low	High
Schwabbauer et al. [28]	Probably low	Probably low	High	Probably low	Probably low	Low	Low

risk reduction, 95% CI 0.6% reduction to 15.7% reduction, low certainty) (Fig. 4). The number needed to treat (NNT) for this outcome is 11 (95% CI 6–167). There was no credible subgroup effect on this outcome based on individual study risk of bias (Fig. 4) or admission location (emergency department or ICU) (Supplementary Fig. 3). Sensitivity analysis excluding one RCT of emergency department patients who were less hypoxemic, and another excluding an RCT with a short duration of follow-up did not change the overall pooled estimates for any of these outcomes (Supplemental Fig. 4, 5, 6).

Compared to conventional oxygen therapy, HFNC use had no effect on ICU length of stay (mean difference [MD] 1.38 days more, 95% CI 0.90 days less to 3.66 days more, low certainty) or hospital length of stay (MD 0.84 days less, 95% CI 2.04 days less to 0.36 days more, moderate certainty) (Supplementary Fig. 7 and 8). Patient reported dyspnea (standardized mean difference [SMD] 0.16 lower, 95% CI 1.10 lower to 1.42 higher, low certainty) and comfort (SMD 0.12 lower, 95% CI 0.61 lower to 0.37 higher, very low certainty) were similar between those receiving HFNC as compared to conventional oxygen therapy (Supplementary Fig. 9 and 10). No other subgroup analysis was possible due to a small number of included studies.

Complications were variably reported across the included studies and this precluded our ability to conduct pooled analysis. Qualitative assessment does not suggest an increased risk of complications in patients receiving HFNC versus conventional oxygen therapy (Table 3).

Discussion

Although our systematic review and meta-analysis did not demonstrate a survival benefit compared with conventional oxygen therapy, HFNC use in patients with acute hypoxemic respiratory failure may decrease the need for tracheal intubation. HFNC had no impact on comfort, dyspnea or ICU/hospital length of stay. In general, dyspnea and comfort are challenging outcomes to assess in critically ill patients. The certainty of evidence for most outcomes was low or moderate, and limited primarily by imprecision and risk of bias of included studies. It remains unclear whether there are certain critically ill patients that may benefit from HFNC more than others. Subgroup analysis based on specific patient characteristics was planned, however, it was not possible due to the small number of studies that reported separate outcome data from these subgroups.

Strengths of this review include a comprehensive literature search, adherence to our pre-registered protocol, focus on only patients with acute hypoxemic respiratory failure, application of GRADE methodology to assess certainty in pooled estimates of effect, and inclusion of a large, recent trial [14] that contributed over half of the patients to this pooled analysis. Limitations include lack of sufficient data to explore relevant subgroup effects, inclusion of only unblinded trials, and outcome data affected by imprecision for most outcomes. Although there was clinical heterogeneity in terms of the types of patients included between studies and authors' definitions of hypoxemia, most outcomes did not demonstrate statistical heterogeneity (i.e. inconsistency). One trial contributed approximately one-third of the data, and this may affect generalizability of results. Also, we were unable to meta-analyze data pertaining to complications due to variations in reporting.

The 4.4% absolute decrease in intubation in those receiving HFNC is important (number needed to treat of 23). This outcome is patient important and the results are consistent with the outcome of escalation of therapy

Table 2 Summary of findings table

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNC	Usual care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 7 days to 90 days; assessed with: longest available)												
4[a]	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	None	187/722 (25.9%)	186/685 (27.2%)	RR 0.94 (0.67 to 1.31)	16 fewer per 1000 (from 90 fewer to 84 more)	⊕⊕⊕ Moderate	Critical
Invasive mechanical ventilation (follow up: range 2 days to 28 days)												
7[c]	Randomised trials	Serious[d]	Not serious	Not serious	Serious[e]	None	205/842 (24.3%)	235/805 (29.2%)	RR 0.85 (0.74 to 0.99)	44 fewer per 1000 (from 76 fewer to 3 fewer)	⊕⊕ Low	Critical
Escalation of therapy (follow up: range 2 days to 28 days; assessed with: any escalation to HFNC, NIV or intubation)												
8[f]	Randomised trials	Serious[d]	Not serious	Not serious	Serious[e]	None	219/871 (25.1%)	266/832 (32.0%)	RR 0.71 (0.51 to 0.98)	93 fewer per 1000 (from 157 fewer to 6 fewer)	⊕⊕ Low	Critical
ICU length of stay (assessed with: days)												
2[g]	Randomised trials	Not serious	Serious[h]	Not serious	Serious[i]	None	494	482	–	MD 1.38 days higher (0.9 lower to 3.66 higher)	⊕⊕ Low	Critical
Hospital length of stay (assessed with: days)												
3[j]	Randomised trials	Not serious	Not serious	Not serious	Serious[i]	None	616	591	–	MD 0.85 days fewer (2.07 fewer to 0.37 more)	⊕⊕⊕ Moderate	Critical
Patient-reported Dyspnea (assessed with: variable score)												
5[k]	Randomised trials	Serious[l]	Not serious[m]	Not serious	Serious[e]	None	458	436	–	SMD 0.66 SD lower (1.68 lower to 0.35 higher)	⊕⊕ Low	Critical
Patient-reported comfort (assessed with: variable score)												
7[n]	Randomised trials	Serious[l]	Serious[o]	Not serious	Serious[b]	None	624	607	–	SMD 0.12 SD lower (0.61 lower to 0.37 higher)	⊕ Very low	Critical

CI Confidence interval; *RR* risk ratio; *MD* mean difference; *SMD* standardised mean difference

[a] Azoulay et al. [14], Frat et al. [24], Jones et al. [25], Makdee et al. [19]

[b] Although point estimate suggests no effect, confidence intervals don't exclude important benefit and important harm

[c] Azoulay et al. [14], Bell et al. [23], Frat et al. [24], Jones et al. [25], Lemiale et al. [20], Makdee et al. [19], Rittayamai et al. [27]

[d] None of the included trials were at low risk of bias for blinding and decision to escalate therapy or intubate may be subjective.

[e] Upper end of 95% confidence interval doesn't exclude no effect

[f] Azoulay et al. [14], Bell et al. [23], Frat et al. [24], Jones et al. [25], Lemiale et al. [20], Makdee et al. [19], Parke et al. [26], Rittayamai et al. [27]

[g] Azoulay et al. [14], Frat et al. [24]

[h] High Isquared and discrepant results among the two studies reporting this outcome

[i] 95% confidence interval doesn't exclude important benefit or harm

[j] Azoulay et al. [14], Jones et al. [25], Makdee et al. [19]

[k] Azoulay et al. [14], Lemiale et al. [20], Makdee et al. [19], Rittayamai et al. [27], Schwabbauer et al. [28]

[l] Subjective outcome in unblinded trial. Also other risk of bias issues in the trials reporting this outcome

[m] High Isquared however all studies show benefit with HFT so did not lower

[n] Azoulay et al. [14], Bell et al. [23], Frat et al. [24], Lemiale et al. [20], Makdee et al. [19], Rittayamai et al. [27], Schwabbauer et al. [28]

[o] High Isquared with variable effect across included studies

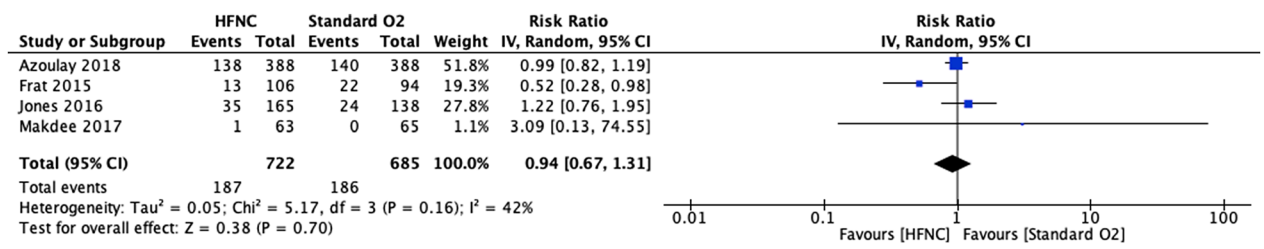

Fig. 2 Mortality forest plot

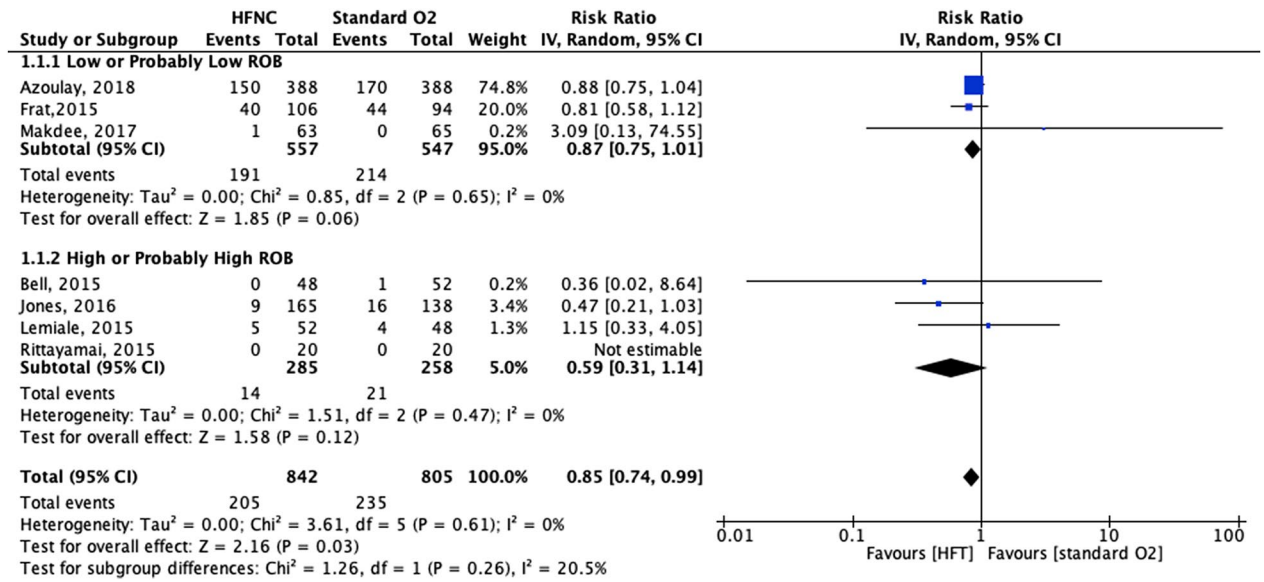

Fig. 3 Need for invasive mechanical ventilation

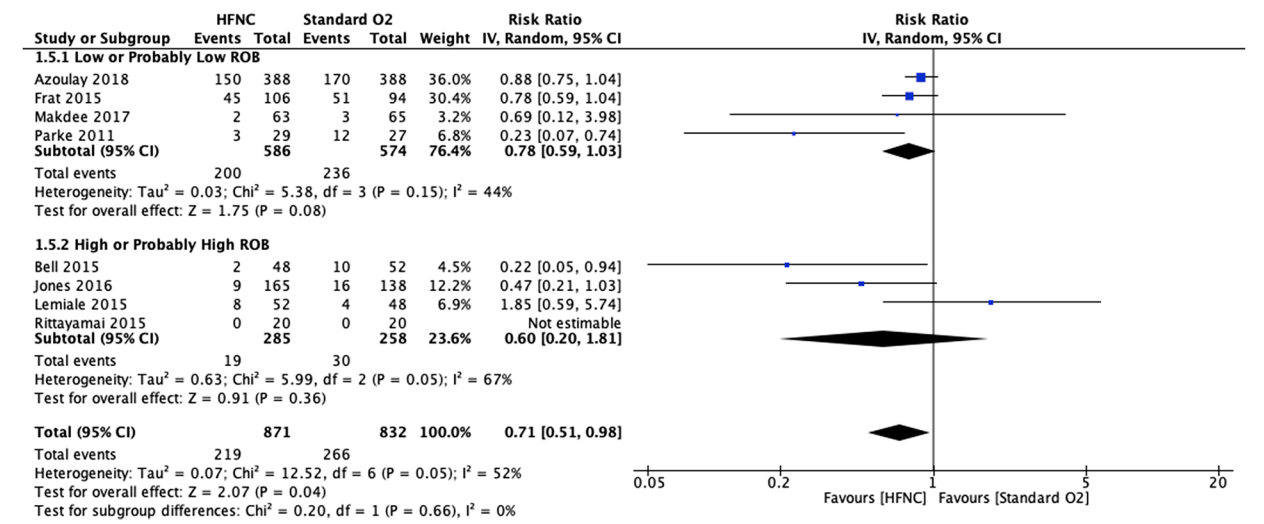

Fig. 4 Escalation of therapy forest plot

Table 3 Complications from included studies

	HFNC	Standard O_2
Makdee et al. [19]	*n* = 63	*n* = 65
Thoracic and cervical discomfort	2	0
Feeling Hot	4	0
Jones et al. [25]	*n* = 165	*n* = 138
Apnea	0	1
Drop in GCS of 2 or more points	1	6
Fall in GCS due to CO2 Retention	0	3
Rittayamai et al. [27]	*n* = 20	*n* = 20
Unpleasant smell	1	0
Temperature too warm	1	0
Chest discomfort	1	0
Frat et al. [24]	*n* = 106	*n* = 94
Cardiac dysrhythmia	11	16
Septic shock	19	26
Cardio-respiratory arrest	5	7
Nosocomial Pneumonia	4	8
Azoulay et al. [14]	*n* = 388	*n* = 388
ICU-acquired infection	39	41

GCS Glasgow coma scale, *HFNC* high flow nasal cannula

Makdee et al. [19] included aspiration and nasal ulceration but no events occurred in either group

Jones et al. [25] included pneumothorax, subcutaneous emphysema and nasal pressure sore, but no events occurred in either group

Bell et al. [23] reported that no adverse events occurred in either group

(a composite of different escalation modalities including escalation to HFNC in the conventional oxygen therapy arm). One potential mechanism of benefit with HFNC in this population is the decreased risk of patient self-inflicted lung injury achieved through more adequately matching the patient's respiratory flow demands [30]. The effect of HFNC on preventing need for intubation is consistent across the included RCTs with minimal statistical heterogeneity. There is more statistical heterogeneity in the mortality outcome data, and although this could be due to important differences in patient populations or the intervention delivered, there were also fewer events for this outcome, increasing the possibility that this could be explained by chance alone. One of the largest predictors of HFNC effect, flow rates, was variably used and reported in the included trials, which may have contributed to the lack of effect seen in some outcomes [31].

Given that HFNC is less invasive, it has been hypothesized that the risk for nosocomial complications, such as pneumonia, clot and delirium, is also lower in HFNC as compared to NIV or invasive mechanical ventilation. Finally, the costs and resources associated with HFNC use are hypothesized to be lower than those associated with more invasive forms of oxygen therapy, although comprehensive cost-effectiveness data are lacking. This being said, there are important caveats to consider. Patients requiring HFNC for acute hypoxemic respiratory failure are at high risk of requiring intubation, and although HFNC is less invasive, it may be falsely reassuring for clinicians. We suggest that patients on HFNC should be monitored closely by appropriately trained clinicians. For patients who fail to improve with HFNC therapy, intubation should be strongly considered.

Although previous meta-analyses have been published examining outcomes with HFNC compared with others forms of oxygen therapy, [9, 12, 13], this is the first since the publication of the HIGH trial [22]. Of the previous reviews, one included 5 RCTs and did not find any effect on escalation of therapy (defined as escalation to HFNC [in the control group], NIV or invasive mechanical ventilation) [12]. Two other reviews demonstrated less need for escalation with HFNC, but included studies of HFNC used in all types of settings including post-extubation and post-operatively [9, 13]. As such, our review, including the most recent study data, is the first to demonstrate improvements with HFNC strictly in patients presenting with acute hypoxemic respiratory failure.

Complications with HFNC are possible, however, they are usually self-limited and do not require discontinuing therapy. Meta-analysis of complication data was not possible as part of this review due to heterogeneous reporting, but rates of major complications were similar in individual RCTs between those receiving HFNC and usual care. Patients treated with HFNC are at risk of fatiguing and therefore its use should be considered a discrete trial with a plan to escalate if they are not improving after a few hours.

Conclusions

Including the most recent published evidence, we have demonstrated that although HFNC does not decrease mortality in those with acute hypoxemic respiratory failure, it may decrease the need for intubation. Our best estimate is a 4.4% absolute reduction in the need for intubation (NNT = 23). Point estimates suggest no effect on patient-reported dyspnea or comfort. Harms with HFNC are likely minimal, at least compared to other more invasive oxygen delivery modalities. Future research should focus on which subgroups of patients with acute hypoxemic respiratory failure are most likely to benefit from HFNC.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05590-5) contains supplementary material, which is available to authorized users.

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Conflict of Interest
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An approval by an ethics committee was not applicable

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