Respiratory Medicine 131 (2017) 58–64

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

Does high-flow nasal cannula oxygen improve outcome in acute hypoxemic respiratory failure? A systematic review and meta-analysis

Si-ming Lin [a], Kai-xiong Liu [b, *], Zhi-hong Lin [a], Pei-hong Lin [a]

[a] Department of Emergency Medicine, The First Affiliated Hospital, Fujian Medical University, 20 Chazhong Road, Fuzhou 350005, China
[b] Department of Respiratory Disease, The First Affiliated Hospital, Fujian Medical University, 20 Chazhong Road, Fuzhou 350005, China

ARTICLE INFO

Article history:
Received 5 March 2017
Received in revised form
16 June 2017
Accepted 7 August 2017
Available online 9 August 2017

Keywords:
High flow nasal cannula
Acute respiratory failure
Meta-analysis
Systematic review

ABSTRACT

Introduction: To evaluate the efficacy of high-flow nasal cannula (HFNC) in the rate of intubation and mortality for patients with acute hypoxemic respiratory failure.
Methods: We searched Pubmed, EMBASE, and the Cochrane Library for relevant studies. Two reviewers extracted data and reviewed the quality of the studies independently. The primary outcome was the rate of intubation; secondary outcome was mortality in the hospital. Study-level data were pooled using a random-effects model when I2 was >50% or a fixed-effects model when I2 was <50%.
Results: Eight randomized controlled studies with a total of 1,818patients were considered. Pooled analysis showed that no statistically significant difference was found between groups regarding the rate of intubation (odds ratio [OR] = 0.79; 95% confidence interval [CI]: 0.60–1.04; P = 0.09; I2 = 36%) and no statistically significant difference was found between groups regarding hospital mortality (OR = 0.89; 95% CI: 0.62–127; P = 0.51; I2 = 47%).
Conclusions: The use of HFNC showed a trend toward reduction in the intubation rate, which did not meet statistical significance, in patients with acute respiratory failure compared with conventional oxygen therapy (COT) and noninvasive ventilation (NIV). Moreover no difference in mortality. So, Large, well-designed, randomized, multi-center trials are needed to confirm the effects of HFNC in acute hypoxemic respiratory failure patients.

Contents

* Corresponding author.
E-mail addresses: 565603150@qq.com (S.-m. Lin), lkxfpt@sina.com (K.-x. Liu).

http://dx.doi.org/10.1016/j.rmed.2017.08.005
0954-6111/

1. Introduction

Good tolerance [1–5], fewer skin breakdown [6], and a lower nurse workload [7] of high-flow nasal cannula (HFNC) has been reported compared with non-invasive ventilation (NIV), Consequently, HFNC is nowadays widely studied in the patients with hypoxemic respiratory failure. HFNC involves delivery of heated and humidified oxygen via special devices (eg, Vapotherm, Comfort Flo, or Optiflow) at rates up to 8 L/min in infants and up to 60 L/min in children and adults [8]. In patients with respiratory distress or failure, humidified high-flow nasal cannula may be better tolerated than oxygen by face mask in terms of comfort and, in observational studies, has been associated with decreased respiratory rate, decreased work of breathing, and better oxygenation in patients of all ages [8–10].

In patients with acute hypoxemic respiratory failure, high-flow oxygen therapy by nasal cannula is a reasonable alternative to standard oxygen therapy or noninvasive positive pressure ventilation. Whether HFNC can reduce the need for intubation or mortality in acute respiratory failure (ARF) patients. The first results were reported in a randomized controlled trial (RCT) which included postoperative cardiac surgery patients with ARF [11]. HFNC patients were less likely to need escalation to noninvasive ventilation (NIV) than those receiving conventional oxygen devices and also had fewer desaturations. More recently, the first large RCT to assess clinical outcomes with HFNC,conventional oxygen devices, and NIV has been published [3]. HFNC group did not result in significantly different intubation rates, but has a significantly difference in 90-day mortality. Additional RCTs including patients with acute hypoxemic respiratory failure have produced conflicting results [2,4,5,7,12–14].

Therefore, we performed a systematic literature review and meta-analysis to determine the effect of the addition of HFNC to standard therapy or NIV on intubation and mortality, using the rate of intubation as the primary outcome, and mortality as secondary outcomes.

2. Materials and methods

2.1. Data sources and search strategy

To identify studies for inclusion in this review, two authors independently searched PubMed, EMBASE, and the Cochrane Central Database of Controlled Trials for relevant studies published up to September 2016. The search was limited to studies conducted with humans. Search terms were individualized for each database. Search terms used included: [‘high-flow nasal cannula’ OR ‘nasal high flow’ OR ‘high-flow nasal oxygen therapy’ OR ‘nasal high-flow oxygen’ OR ‘high-flow nasal oxygen’ OR ‘humidified high-flow nasal cannula’ OR ‘heated and humidified high-flow nasal oxygen’ OR ‘Optiflow’ OR ‘Vapotherm’ OR ‘Comfort Flo’] AND [‘respiratory insufficiency’ OR ‘acute respiratory failure’ OR ‘acute respiratory distress syndrome’ OR ‘Ventilatory Depression’ OR ‘dyspnea’]. We also searched the proceedings of major relevant conferences, trial databases, the reference lists of identified trials, and major reviews. We had no language restrictions.

2.2. Study selection

Two reviewers (S.M. Lin and K.X. Liu) independently screened studies for inclusion, retrieved potentially relevant studies, and determined study eligibility. Any discrepancies were resolved by consensus. Analysis was restricted to randomized controlled trials (RCTs). For this meta-analysis, we considered those RCTs that compared administration of HFNC vs conventional oxygen therapy (COT) and noninvasive ventilation (NIV) in acute hypoxemic respiratory failure and not requiring immediate ventilatory support patients (such as those admitted to an ICU or emergency department), and which reported the incidence of the rate of intubation, or mortality.

2.3. Data extraction

Two authors independently extracted data from all of the enrolled studies. Extracted data included study design (e.g., year conducted, sample size), patient characteristics, study methodology (e.g., eligibility criteria, method of randomization, and blinding), intervention (e.g., gas flow rate, FIO2), and clinical outcomes (e.g., incidence of the rate of intubation, mortality, tolerability,comfort). Differences in opinion were settled by consensus or after consultation with a third investigator.

2.4. Quality assessment

We formally assessed the methodological quality of each trial using the “risk of bias” tool within RevMan Review Manager, Version 5.3. Random sequence generation, allocation concealment, blinding, incomplete data, and selective reporting were assessed; based on the method of the trials, each was graded “yes,” “no,” or “unclear,” which reflected a high risk of bias, low risk of bias, and uncertain bias, respectively. Two reviewers (S.M. Lin and K.X. Liu) independently appraised the quality of the included trials.

2.5. Statistical analysis

The meta-analysis was done using Revman version 5.3 for Windows. We computed pooled odds ratios (OR) and 95% confidence intervals (CI) from the adjusted ORs and 95% CIs reported in the RCT studies. We used the chi-square test and I2 statistics to assess the heterogeneity of study results. We predefined heterogeneity as low, moderate, and high with I2 values of above 25%, 50%, and 75%, respectively. In the analysis of heterogeneity, we considered a P value < 0.10 to be statistically significant. Study-level data were pooled using a random-effects model when I2 was >50% or a fixed-effects model when I2 was <50%.Publication bias was assessed by a funnel plot using the need for intubation as an endpoint.

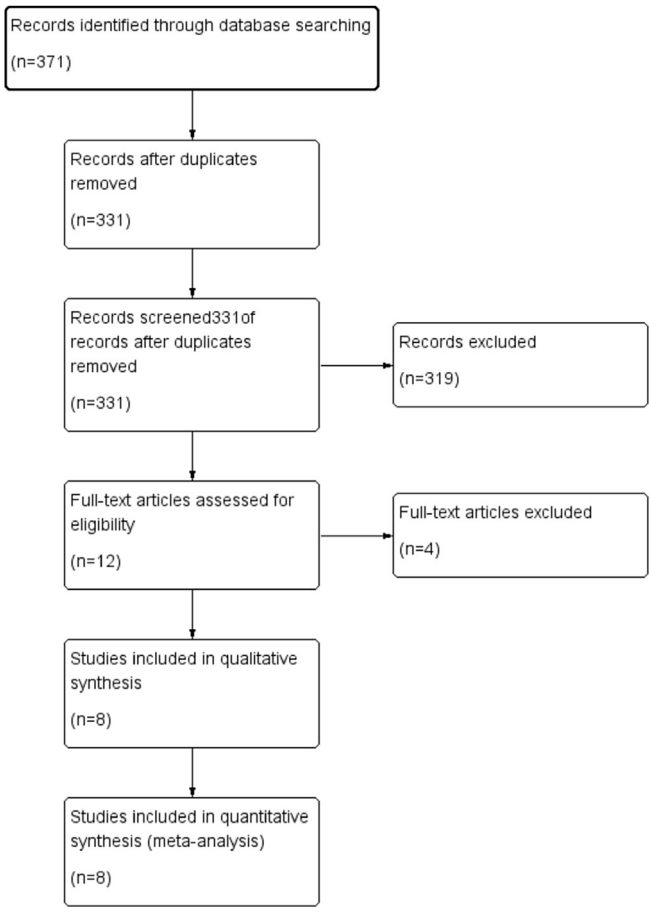

Fig. 1. Flow of study selection.

3. Results

Our search retrieved a total of 371references. After applying the inclusion criteria, 8 studies were included in this meta-analysis [2–5,7,12–14]. A flow chart for the studies evaluated and the reasons for exclusion are shown in Fig. 1.

3.1. Study characteristics

Characteristics of the included studies are summarized in Table 1. A total of 1818 patients were included in these studies. All studies were published from 2014 to 2015. Although all eight trials were published in English, they represent an international experience. Four were multiple-center trials [2–4,7], whereas the remaining four were conducted in a single center [5,12–14]. Five studies recruited patients in ICUs [3,4,7,13,14], three studies recruited patients in the emergency department [2,5,12], two studies recruited patients who in ARF after extubation [4,7], one study recruited patients who had undergone cardiothoracic surgery [7], one study recruited patients in immunocompromised with hypoxemic acute respiratory failure [13]. In one trial patients were randomly assigned to one of the three following strategies: high-flow oxygen therapy, standard oxygen therapy, or noninvasive ventilation [3]. In another two trials attending physicians randomly assigned patients to one of the 2 groups: high-flow humidified oxygen, noninvasive ventilation [7,14]. Five trial patients were randomly assigned to one of the two following strategies: high-flow oxygen therapy, standard oxygen therapy [2,4,5,12,13]. From the trial publications, or through author contact, we obtained data from eight trials on the need for intubation [2–5,7,12–14], four trials on hospital mortality [3,4,7,12], and four trials not relevant mortality [2,5,13,14]. The risks of bias summary in individual studies has been shown in Fig. 2.

3.2. Intubation

Results from 8 trials (1818 patients) were available to examine the effects of HFNC on the incidence of intubation. A low level of heterogeneity was found among the identified comparisons ($I2 = 36\%$; $P = 0.16$). Pooled analysis showed that compared with the control group (standard oxygen group and noninvasive ventilation group), the use of HFNC showed a trend toward reduction in the rate of intubation, which did not meet statistical significance, in acute hypoxemic respiratory failure patients (OR = 0.79; 95% CI: 0.60–1.04; P = 0.09) (Fig. 3). We also compared with the standard oxygen group or noninvasive ventilation group separately. Compared with the standard oxygen group only, the use of HFNC was associated with statistically significant reduction in the incidence of intubation in acute hypoxemic respiratory failure patients

Table 1
Characteristics of the study in various studies.

Study	Design	Setting	Population	Regimen used	Intubation n/N	Mortality n/N
Azevedo et al., 2015	SC RCT	surgical ICU	ARF(n = 30)	HFNC (n = 14) NIV (n = 16)	HFNC:6/14 NIV:6/16	NA
Bell et al., 2015	MC RCT	ED	ARF(n = 100)	HFNC (n = 48) COT (n = 52)	HFNC:0/48 COT:1/52	NA
Frat et al., 2015	MC RCT	Medical ICU	ARF(n = 310)	HFNC(n = 106) COT(n = 94) NIV(n = 110)	HFNC:40/106 COT:44/94 NIV:55/110	HFNC:12/106 COT:18/94 NIV:27/110
Jones et al., 2015	SC RCT	ED	ARF(n = 303)	HFNC (n = 165) COT (n = 138)	HFNC:1/165 COT:3/138	HFNC:15/165 COT:11/138
Lemaile et al., 2015	SC RCT	General ICU	ARF immunocompromised patients (n = 100)	HFNC (n = 52) COT (n = 48)	HFNC:4/52 COT:2/48	NA
Maggiore et al., 2014	MC RCT	General ICU	ARF postextubation (n = 105)	HFNC (n = 53) COT (n = 52)	HFNC:2/53 COT:11/52	HFNC:6/53 COT:5/52
Rittayami et al., 2015	SC RCT	ED	ARF(n = 40)	HFNC (n = 20) COT (n = 20)	HFNC:0/20 COT:0/20	NA
Stephan et al., 2015	MC RCT	Cardiac ICU	ARF Postextubation (n = 830)	HFNC(n = 414) NIV(n = 416)	HFNC:58/414 NIV:57/416	HFNC:28/414 NIV:23/416

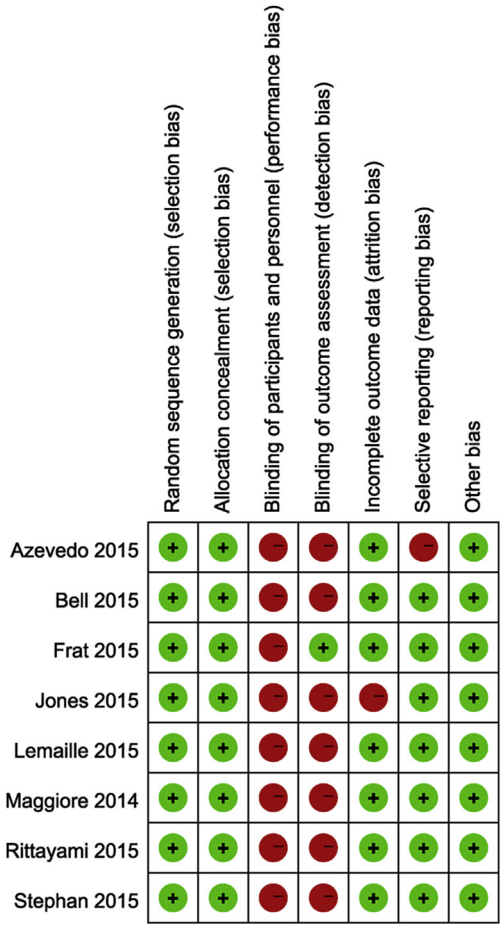

Fig. 2. The risks of bias summary in individual studies.

(OR = 0.58 95% CI: 0.36–0.92; P = 0.02; I2 = 29%)(Fig. 4). Compared with the noninvasive ventilation group only, the use of HFNC was not associated with statistically significant reduction in the incidence of intubation (OR = 0.87; 95% CI: 0.64–1.19; P = 0.38; I2 = 24%) (Fig. 5).

3.3. Mortality

Mortality was reported in four trials, including 1548 patients, one of which reported a survival advantage and three of which found no difference. We choose the hospital mortality as a statistical basis. After we pooled study results, HFNC had no effect on overall mortality (OR = 0.89, 95% CI: 0.62–1.27; P = 0.51; I2 = 47%) (Fig. 6).

3.4. Dyspnea

Six studies reported the effect HFNC on dyspnea compared with the control group (standard oxygen group and noninvasive ventilation group) [2,3,5,7,12,13]. Three studies reporting this parameter did not find any difference between the groups [7,12,13]. Whereas, the other three studies reported significantly reduced dyspnea when HFNC was compared with the control group [2,3,5].

3.5. Comfort

Seven studies reported an assessment of comfort level of HFNC and control groups [2–5,7,12,13]. Four studies showed significantly improved comfort scores compared with COT [2–5] or NIV [3]. Two studies did not find any difference in the comfort level of HFNC and control groups [7,13]. But one study found the COT group felt more comfortable than the HFNC group [12].

4. Discussion

Our meta-analysis found that the early application of HFNC had a trend toward reduction in the incidence of intubation in patients presenting with acute hypoxemic respiratory failure, which is not statistically significant. But compared with the standard oxygen group alone, HFNC reduced the rate of intubation (absolute risk reduction 42%,95% CI: 0.36–0.92; P = 0.02), as a post hoc analysis, this finding must be interpreted with caution. This potential benefit can be explained by the following mechanisms: reduced anatomical dead space [11,15–19], a low level of positive end-expiratory pressure [20,21], improved thoracoabdominal synchrony [22], and decreased symptoms of mucosal dryness [17,23], and increased patient tolerance [24,25]. Frat et al. [3]found that when compared with NIV or COT in adult

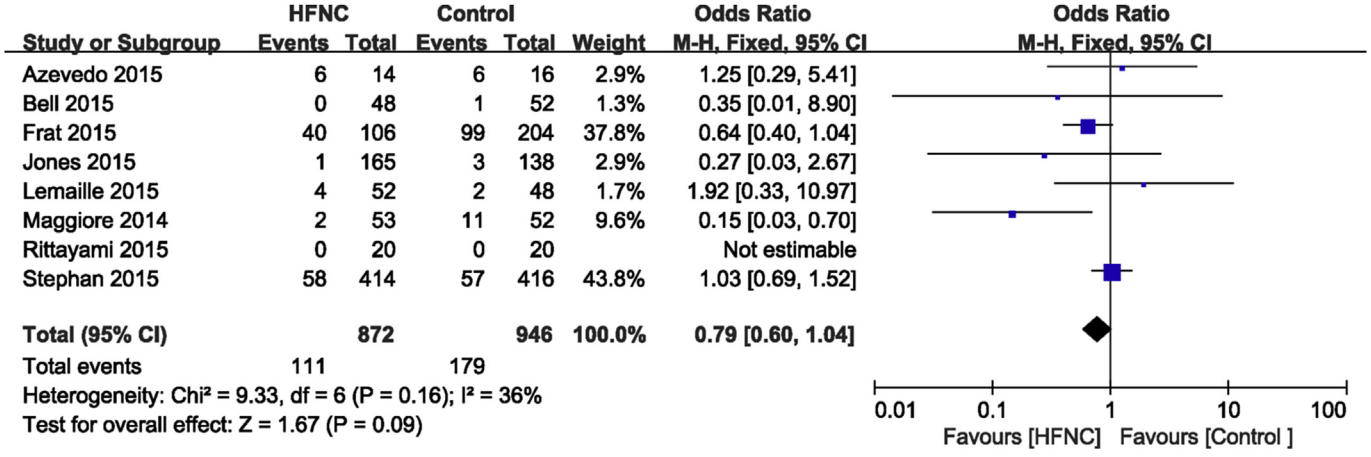

Fig. 3. Forrest plot comparing intubation rates in patients treated with HFNC compared with COT and NIV.

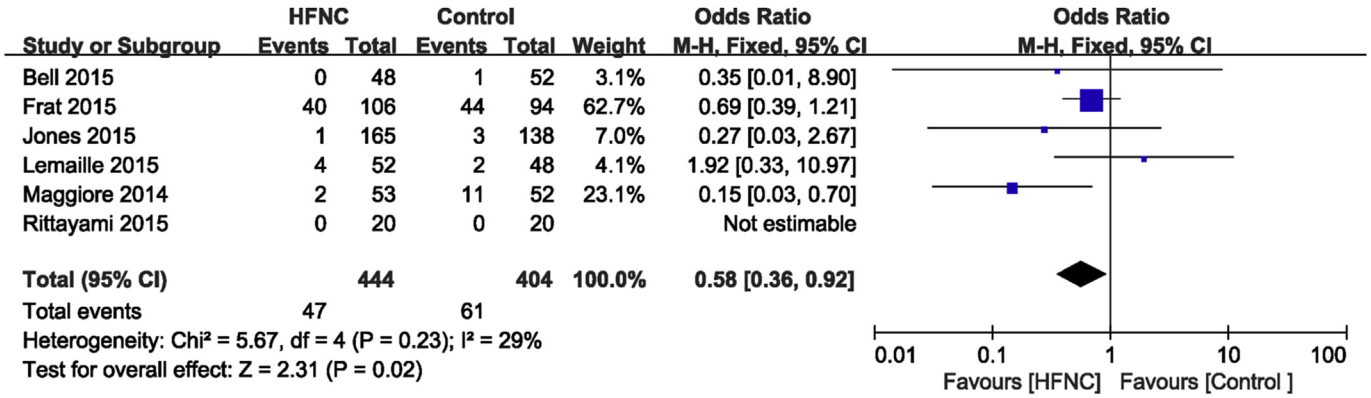

Fig. 4. Forrest plot comparing intubation rates in patients treated with HFNC compared with COT only.

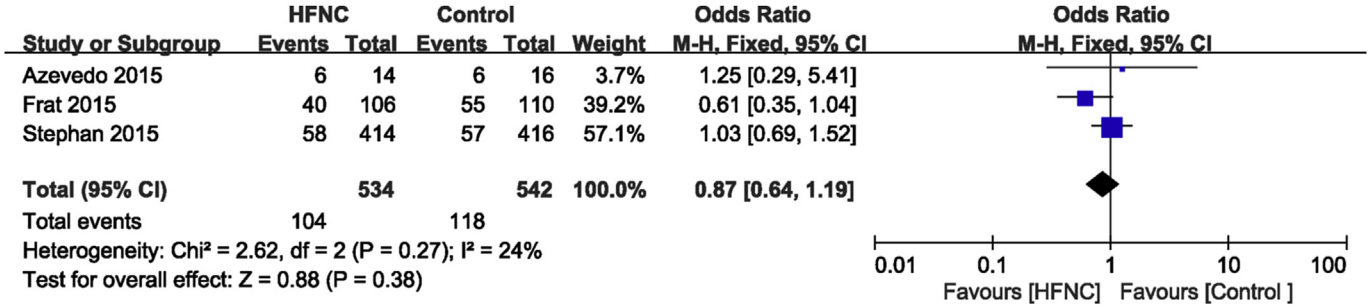

Fig. 5. Forrest plot comparing intubation rates in patients treated with HFNC compared with NIV only.

patients with ARF, HFNC did not demonstrate a reduction in the intubation rate, but a post hoc adjusted analysis including the 238 patients with a PaO2/FIO2 ratio ≤200 mmHg found that HFNC reduced intubation rates (P = 0.009). Jones et al. [12] reported some severely hypoxic patients were excluded from the study because clinicians were not comfortable with delaying NIV even for 30 min to deliver the study interventions. Therefore, it is possible that the included study participants were not as severely unwell as the pilot study population. So more attention should be paid to find the interaction between Pao2:Fio2 stratum and treatment.

Meanwhile, the pooled results showed that HFNC did not affect hospital mortality, the secondary endpoints to the study. Only one study [3] show a significant difference in favor of high-flow oxygen in mortality. The remainder RCTs suggested that no statistically significant difference was found between groups regarding hospital mortality. These findings might result from that time to intubation may be delayed in patients treated with HFNC [26]. This might lead to increased mortality in some patients [27]. The study by Kang et al. [27] also show that early intubation associated with better ICU survival. So, it is important to get the ability to describe the success of HFNC treatment which can allow timely intubation in patients who are likely to fail. Other potential mechanism is the possibility of oxygen toxicity [28].

Although many aspects of HFNC therapy remain unclear, evidence supporting its use in hypoxemic ARF patients is accumulating steadily. In future research patient selection should be individualized and such patients should be cared for in a monitored environment, preferably in an ICU. If improvement is not seen soon after implementation, intubation and conventional mechanical ventilation should be implemented without delay. Meanwhile, with the evidence currently available, decisions on

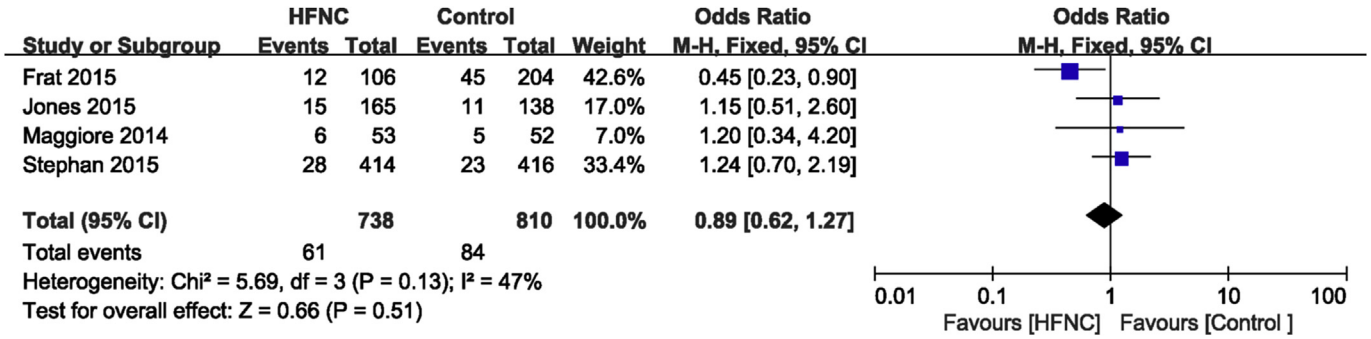

Fig. 6. Forrest plot comparing mortality rates in patients treated with HFNCcompared with COT and NIV.

HFNC treatment should be individualized in each particular situation [8].

The strengths of this review include a systematic approach to searching the literature and avoidance of language and publication bias. Trials of any type of patients with acute hypoxemic respiratory failure were eligible for our study, and therefore our results are applicable across a wide range of clinical situations. Independently and in duplicate, we selected studies and assessed trial validity using specific criteria.

Our analysis has several limitations. First, there was heterogeneity in the inclusion criteria, the populations studied, the variable duration of the treatment, titration of oxygen concentrations, and different flow rate of oxygen between studies. These factors were not comparable in most of the trials and might have affected the clinical outcomes. These differences may explain the statistical heterogeneity. Second, even though we were able to pool results across all trials, the number of patients included in this meta-analysis may not be sufficient to exclude any significant clinical benefits. Finally, the quality of the included studies was not consistent. The quality of trials can affect the direction and magnitude of treatment effects when doing a meta-analysis.

Although the results have been depressing, there is insufficient evidence to suggest to clinicians that HFNC is associated with significant clinical benefits in patients with acute hypoxemic respiratory failure, but a trend toward reduction in the intubation rate had been showed. So the questions that remain to be evaluated in large-scale, randomized controlled trials of HFNC use for ARF include to describe the success of HFNC treatment, to establish the optimal flow rate to set up in each patient, safety, patient eligibility, and contraindications.

5. Conclusions

This systematic review of RCTs of patients with acute hypoxemic respiratory failure suggests that the use of HFNC showed a trend toward reduction in the intubation rate, which did not meet statistical significance compared with COT or NIV, and no improvement in mortality. Large, well-designed, randomized, multi-center trials are needed to confirm the effects of HFNC in acute hypoxemic respiratory failure patients.

Acknowledgements

No funding bodies played any role in study design, data collection and analysis, decision to publish, or preparation this manuscript.

Abbreviations

ARF	acute respiratory failure
COT	conventional oxygen therapy
ED	emergency department
HFNC	High flow nasal cannula
ICU	intensive care unit
MC	multicenter
NA	not available
NIV	noninvasive ventilation
RCT	randomized controlled trial
SC	single-center

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SML and KXL carried out primary study search, extracted data, performed statistical analysis and drafted/revised the manuscript. SML carried out statistical analysis and revised the manuscript. ZHL revised the manuscript and modified the English writing. PHL conceived the idea, participated in its design and drafted/revised the manuscript. All the authors gave their final approval to the version submitted for publication.

Conflict of interest statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, “Does high-flow nasal cannula oxygen improve outcome in acute hypoxemic respiratory failure? A systematic review and meta-analysis”.

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