High-Flow Nasal Cannula in Hypercapnic Respiratory Failure: A Systematic Review and Meta-Analysis

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Background. Although the efficacy and safety of high-flow nasal cannula (HFNC) in hypoxemic respiratory failure are widely recognized, it is yet unclear whether HFNC can effectively reduce the intubation rate and mortality in hypercapnic respiratory failure. We performed a systematic review and meta-analysis to assess the safety and efficiency of HFNC in these patients.

Methods. A systematic search of PubMed, Embase, and Cochrane Library (CENTRAL) was carried out. Two reviewers independently screened all references according to the inclusion criteria. We used the Cochrane risk-of-bias tool and the Newcastle–Ottawa Quality Assessment Scale to assess the quality of randomized controlled trials (RCTs) and cohort studies, respectively. Data from eligible trials were extracted for the meta-analysis. Results. Eight studies with a total of 621 participants were included (six RCTs and two cohort studies). Our analysis showed that HFNC is noninferior to noninvasive ventilation (NIV) with respect to intubation rate in both RCTs (OR = 0.92, 95% CI: 0.45–1.88) and cohort studies (OR = 0.94, 95% CI: 0.55–1.62). Similarly, the analysis of cohort studies showed no difference in reducing mortality rates (OR = 0.96, 95% CI: 0.42–2.20). Based on RCTs, NIV seemed more effective in reducing mortality (OR = 1.33, 95% CI: 0.68–2.60), but the intertreatment difference was not statistically significant. Furthermore, no significant differences were found between HFNC and NIV relating to change of blood gas analysis or respiratory rate (MD = −0.75, 95% CI: −2.6 to 1.09). Likewise, no significant intergroup differences were found with regard to intensive care unit stay (SMD = −0.07, 95% CI: 0.26 to 0.11). Due to a physiological friendly interface and variation, HFNC showed a significant advantage over NIV in patients’ comfort and complication of therapy. Conclusion. Despite the limitations noted, HFNC may be an effective and safe alternative to prevent endotracheal intubation and mortality when NIV is unsuitable in mild-to-moderate hypercapnia. Further high-quality studies are needed to validate these findings.

1. Introduction

Respiratory failure, which can occur due to several different diseases and conditions, is a common syndrome occurring in the intensive care unit (ICU) [1]. Endotracheal intubation is usually performed only when the patient is deteriorating despite optimal drug and common oxygen therapy, and it often results in extra medical expenses, longer hospital stay, and even higher mortality [2, 3]. Thus, it is crucial to protect patients from acute respiratory failure and avoid, as far as possible, invasive mechanical ventilation.

Noninvasive ventilation (NIV) is recommended by guidelines to avoid intubation and improve outcomes [4]. However, many patients who need respiratory support may be excluded by the technicians for comorbidities such as emphysema and oversecretion of sputum [5, 6]. Besides the contraindications, higher expenditure and numerous potential adverse events are presented during NIV, such as skin damage, eye irritation, interface intolerance, diet, and sputum retention, which cause discomfort and may lead to the termination of NIV to some extent [7].

High-flow nasal cannula (HFNC) is a simple system composed of an air-oxygen blender, active heated humidifier, single heated circuit, and nasal cannula and can deliver high-rate humidified oxygen (up to 60 L/min) through a nasal cannula. It has been deemed an effective and less costly alternative among children to alleviate respiratory distress and prevent extubation failure [8, 9]. In recent years, HFNC...
has become increasingly popular in the treatment of respiratory failure in adults [10]. HFNC is reportedly superior to conventional oxygen therapy and can be as effective as NIV in patients with acute hypoxemic respiratory failure [11]. However, it is still unclear whether HFNC is an effective tool to reduce the intubation rate and mortality in patients suffering from hypercapnic respiratory failure.

2. Methods

This systematic review and meta-analysis was registered at PROSPERO (http://www.crd.york.ac.uk/prospero; CRD: 42020173744) and designed as per the Cochrane Handbook for Systematic Reviews of Interventions [12] and reported according to the PRISMA guidelines.

2.1. Literature Searching Strategy. We performed a comprehensive search of electronic databases including PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) up to May 2020, using the keywords and their synonyms, and the search was updated on September 12, 2020. Terms were related to the intervention and modified according to each database’s index term, such as Medical Subject Heading (MeSH) and Emtree. No language restrictions or publication year were applied when searching PubMed and CENTRAL, while it was limited to clinical studies on humans on Embase. Relevant citations from the references listed in each identified study were also taken into consideration for eligibility. Detailed search terms are shown in Appendix 1 (Supplementary Materials (available here)).

2.2. Inclusion and Exclusion Criteria. Studies in our review had to meet all of the following criteria:

(1) Type of participants: participants must be adults (age >16 years) with acute hypercapnic respiratory failure (PaCO₂ > 45 mmHg)

(2) Type of intervention and comparator: comparing HFNC with NIV

(3) Type of studies: a randomized controlled trial (RCT) or a cohort study

(4) Containing any one of the following outcomes: intubation rate; mortality; blood gas analysis (arterial partial pressure of oxygen (PaO₂), arterial partial pressure of carbon dioxide (PaCO₂), and pH); respiratory rate, patient comfort; and complication of the therapy

Exclusion criteria:

(1) Studies with the same data or overlapping data by the same authors

(2) Studies without any one of the predetermined outcomes

2.3. Quality Assessment. The quality of all selected studies was assessed independently by two reviewers (HYK and ZYW). RCTs were evaluated according to the Cochrane risk-of-bias tool which includes the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. On the contrary, a cohort study was graded according to the Newcastle–Ottawa Quality Assessment Scale [13] with regard to selection, comparability, and outcome.

2.4. Data Extraction. Two researchers (HYK and ZYW) independently extracted the following data from each study: characters of the study (first author, publication year, country, number of participants, case source, cause of hypercapnic respiratory failure, and major inclusion criteria); characters of the participants (demographic variation and basic blood gas analysis); and the primary and secondary outcomes. Any disagreements between the two authors were resolved by consensus or cross-checking with a third author (LW). Additional information was collected through communication with the principal investigator by email if necessary.

2.5. Data Analysis. Statistical analysis was performed by an independent researcher adept in statistics using Cochrane systematic review software Review Manager (RevMan; version 5.4.0; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014). Continuous variables were reported as mean and standard derivation (SD), while dichotomous variables were shown as frequency or proportion. The results were displayed in forest plots. An initial test for clinical, methodological, and statistical heterogeneities was conducted, and we used the chi-square test with \( P < 0.1 \) and \( I^2 > 50\% \) to indicate statistical significance. Random-effect model was applied in the presence of statistical heterogeneity; otherwise, the fixed-effect model was chosen. For continuous data, we calculated the mean difference (MD) or standard mean difference (MD) and 95% confidence interval (CI), and for dichotomous data, we calculated the odds ratio (OR) and 95% CI.

3. Results

3.1. Study Selection and Characteristics. In all, 595 citations were retrieved through literature search. We excluded 150 duplicates identified by the title and authors and omitted 423 studies that did not fulfill the inclusion criteria. We tried to obtain the full text of the remaining 22 searches. Finally, eight studies, comprising six parallel RCTs [14–19] and two cohort studies [20, 21], involving 621 participants were enrolled in the analysis. The flowchart of the study is shown in Figure 1.

Tan et al. conducted their study in two large tertiary care hospitals, while the remaining studies included were all carried out in a single center. Seven studies were performed in Asia and one in Greece. Most patients were admitted to the ICU or respiratory ICU. Three of six RCTs recruited only extubated patients, while patients with acute-exacerbation chronic obstructive pulmonary disease (AECOPD) were the main cause of hypercapnic respiratory failure in another two
RCTs and both cohort studies. One study did not mention the cause of admittance. Characteristics of the participants and studies are shown in Tables 1–3, respectively.

3.2. Risk of Bias within Studies. Three studies [15, 16, 18] did not detail the method of their random sequence generation and allocation concealment, which may cause selection bias. Blinding of participants was not performed in all RCTs owing to different appearances of the devices. There was no bias in detection, attrition, and reporting. The quality assessment of each eligible trial is shown in Figure 2.

3.3. Clinical Effectiveness

3.3.1. Effect on Intubation Rate and Mortality. Both cohort studies and five RCTs that reported intubation and mortality were considered in our meta-analysis. The pooled data showed that HFNC was noninferior to NIV in preventing intubation or reintubation both in RCTs (OR = 0.92, 95% CI: 0.45–1.88) and cohort studies (OR = 0.94, 95% CI: 0.55–1.62). Similarly, the synthesis of cohort studies (OR = 0.96, 95% CI: 0.42–2.20) in reducing mortality indicates no difference. NIV seems to be more effective in reducing mortality in RCTs (OR = 1.33, 95% CI: 0.68–2.60), but the between-treatment difference was not statistically significant. Forest plot of intubation and mortality is shown in Figure 3.

3.3.2. Effect on Blood Gas Analysis and Respiratory Rate. Of all eligible studies, seven reported at least one of the following blood gas analysis outcomes including PaO\textsubscript{2}, PaCO\textsubscript{2}, and pH. The variables at 12 h or 24 h after initiation of therapy were collected and merged.

There was no difference between HFNC and NIV in oxygenation improvement (MD = 0.35, 95% CI: −1.18 to 1.89 in PaO\textsubscript{2} and MD = −5.05 95% CI: −28.06 to 17.97 in PaO\textsubscript{2}/FiO\textsubscript{2}); removing carbon dioxide (MD = −0.02, 95% CI: −2.62 to 2.59 for RCTs; MD = 2.94, 95% CI: −0.20 to 6.07 for cohort studies); pH change (MD = −0.01, 95% CI: −0.03 to 0.01); or alleviating respiratory distress (MD = −0.75, 95% CI: −2.6 to −1.09).
### Table 1: Characteristics of cohort studies.

| Authors, year | Participates of the cohort (HFNC/NIV) | Case source | Follow-up (days) | Location | Major inclusive criteria | Initial indications of HFNC | Initial indications of NIV | Primary outcome | NOS scores |
|---------------|---------------------------------------|-------------|-----------------|----------|--------------------------|----------------------------|----------------------------|-----------------|-----------|
| Sun et al., 2019 | 39/43 ICU | AECOPD or pulmonary infection with COPD | 28 | China | COPD or acute respiratory failure by a secondary diagnosis of COPD with a respiratory acidosis (pH ≤ 7.35 and P_{CO2} ≥ 50 mmHg) | Initial FiO\textsubscript{2} in the HFNC group was 0.3 (0.2–0.4), and the gas flow rate was 50 L/min (40–50). | Initial FiO\textsubscript{2} in the NIV group was 0.4 (0.3–0.6), inspiratory airway pressure was 10 cm H\textsubscript{2}O (8–12), and expiratory airway pressure was 4 cm H\textsubscript{2}O (4–5). Mean expiratory tidal volume during the first 24 hrs of NIV treatment was 5.4 ± 2.4 ml/kg of predicted body weight. | Treatment failure and 28-day mortality | 5 |
| Lee et al., 2018 | 44/44 Respiratory ward | AECOPD | 30 | South Korea | AECOPD with moderate hypercapnic acute respiratory failure ((PaO_{2})/FiO\textsubscript{2} < 200 mmHg, Pa_{CO2} > 45 mmHg, and 7.25 < pH < 7.35 on room air) | Beginning with FiO\textsubscript{2} > 50% and a flow of 35 L/min and then titrating flow to 45–60 L/min if tolerated. FiO\textsubscript{2} was subsequently adjusted to maintain an oxygen saturation of 92% or more. | The expiratory pressure was set at 5 cm H\textsubscript{2}O pressure, and inspiratory pressure was initially set at 10 cm H\textsubscript{2}O and then increased in increments of 2–4 to 20 cm H\textsubscript{2}O or the maximum tolerated over 1 hour. The BiPAP level was adjusted to maintain an oxygen saturation of 92% or more. | Intubation rate and 30-day mortality | 6 |
### Table 2: Characteristics of the RCTs.

| Authors, year | Case source | Subjects | Major inclusive criteria | Follow-up (days) | Location | Outcome | Indications of HFNC | Indications of NIV | Trial registration number |
|---------------|-------------|----------|--------------------------|------------------|----------|---------|---------------------|---------------------|--------------------------|
| Jing et al., 2018 | — | 42 | Patients with hypercapnia (PaCO₂ > 45 mmHg) at the time of extubation and met the “pulmonary infection control window” criteria | 28 | China | The primary outcome parameters were ABG analysis and vital signs. Secondary outcomes included duration of respiratory support, length of ICU stay, the patients' comfort score, and incidence of adverse events. | The humidifier temperature was set at 37°C, and the fraction of inspired oxygen was adjusted to maintain oxygen saturation recorded by pulse oximetry (SpO₂) at 88–92%. | The IPAP was initiated at 10–12 cm H₂O, EPAP started at 4–5 cm H₂O, and subsequent adjustments were based on the patients' ABGs. | ClinicalTrials (NCT03458364) |
| Yu et al., 2019 | ICU | 72 | Extubation patients with hypercapnia (PaCO₂ > 50 mmHg) | Not mentioned | China | The ABG, respiratory rate, heart rate, mean arterial pressure, reintubation rate, mortality, intensive care unit stay, and incidence of adverse events. | The humidifier temperature was set at 37°C, and the fraction of inspired oxygen was adjusted according to ABGs and patients' symptoms and signs. | The IPAP was initiated at 10 ~ 14 cm H₂O, and EPAP was 4 ~ 6 cm H₂O. Variables were adjusted according to ABGs and patients' symptoms and signs. | No |
| Wang et al., 2019 | RICU | 43 | AECOPD patients with hypercapnic respiratory failure | 28 | China | The treatment failure rate, tracheal intubation rate, complications, and 28-day survival rate. | Both the flow rate and the fraction of inspired oxygen were according to ABGs and patients' symptoms and signs. | Both IPAP and EPAP were adjusted according to ABGs and patients' symptoms and signs. | No |
| Cong et al., 2019 | ICU | 168 | AECOPD patients | Not mentioned | China | The primary endpoint was ABG analysis. Secondary clinical endpoints included ventilation support time, hospitalization days and complications, comfort, and nursing satisfaction. | The air temperature was set at 37°C at a flow rate of 30–35 L/min. | The IPAP was set at 10 cm H₂O, and EPAP was set at 5 cm H₂O at the beginning and gradually increased after the patient adapted. Patients' symptoms and signs were monitored, and FiO₂ was adjusted to ensure oxygen saturation. | No |
Table 2: Continued.

| Authors, year | Case source | Subjects | Major inclusive criteria | Follow-up (days) | Location | Outcome | Indications of HFNC | Indications of NIV | Trial registration number |
|---------------|-------------|----------|--------------------------|------------------|----------|---------|---------------------|----------------------|--------------------------|
| Tan et al, 2020 | ICU | Extubation patients with COPD patients with hypercapnic respiratory failure | 28 | China | The primary endpoint was treatment failure. Secondary outcomes included arterial blood gas analysis and vital signs. | | | The initial airflow was set at 50 L/min and adjusted according to patient tolerance. The HFNC was set to an absolute humidity of 44 mg H₂O/L, temperature was set to 37°C, and FiO₂ was adjusted to maintain an SpO₂ of 88–92%. | | Chictr.org (ChiCTR1800018530) |
| Papachatzakis et al., 2020 | ED | Patients suffering acute respiratory failure type 2 | Not mentioned | Greece | Endpoints were intubation and mortality rate, length of hospitalization, duration of therapy, and possible differences between vital signs, ABGs, and comfort. | | | The initial airflow was set at a flow of 35 L/min, titrating flow upward if tolerated to 45–50 L/min, in order to maintain SaO₂ > 90% or according to specific clinical orders. | | No |

ED: emergency department; IPAP: inspiratory positive airway pressure; EPAP: expiratory pressure airway pressure; ABG: arterial blood gases.
Table 3: Characteristics of the participants.

| Authors, year | Age (years) ± SD | Gender (male/total) | APACHE II score (HFNC/NIV) | Respiratory rates (times/minute) (HFNC/NIV) | pH (HFNC/NIV) | PaO₂ (mmHg) or PaO₂/FiO₂ *(mmHg) (HFNC/NIV) | PaCO₂ (mmHg) (HFNC/NIV) | Respiratory support duration (days or hours *) (HFNC/NIV) |
|---------------|------------------|---------------------|-----------------------------|----------------------------------------------|--------------|---------------------------------------------|--------------------------|----------------------------------------------------------|
| Jing et al., 2018 | 77.4 ± 6.8 | 73.9 ± 6.9 | 7/22 | 1/20 | 11.8 ± 3.1 | 10.425 | 18.3 ± 3.5 | 19.2 ± 4.1 | 7.46 ± 0.04 | 7.44 ± 0.06 | 235.8 ± 77.0 * | 250.8 ± 75.8 * | 52.4 ± 6.4 | 53.7 ± 8.6 | 2.73 ± 1.95 | 4.07 ± 4.40 |
| Yu et al., 2019 | 62.4 ± 10.1 | 63.5 ± 11.2 | 24/36 | 21/36 | 28.6 ± 2.8 | 28.5 ± 3.4 | 32 ± 4.4 | 33 ± 4.3 | 7.26 ± 0.03 | 7.26 ± 0.03 | 56.84 ± 2.77 | 56.92 ± 2.89 | 73.56 ± 6.9 | 73.5 ± 6.23 | — | — |
| Wang et al., 2019 | 71.26 ± 7.39 | 72.85 ± 6.65 | 13/23 | 12/20 | 18.35 ± 2.19 | 18.92 ± 2.59 | 30.91 ± 2.13 | 30.35 ± 2.68 | 7.23 ± 0.19 | 7.24 ± 0.02 | 57.17 ± 5.68 | 59.55 ± 6.48 | 67.13 ± 4.25 | 66.05 ± 3.03 | 7.96 ± 1.72 | 6.8 ± 1.26 |
| Cong et al., 2019 | 66.91 ± 7.38 | 67.88 ± 8.38 | 48/84 | 50/48 | — | — | — | — | 7.25 ± 0.08 | 7.27 ± 0.09 | 53.10 ± 16.22 | 54.08 ± 15.33 | 72.11 ± 16.31 | 72.91 ± 16.41 | 10.02 ± 1.11 | 9.55 ± 4.78 |
| Tan et al., 2020 | 68.4 ± 9.3 | 71.4 ± 7.8 | 27/44 | 23/42 | 14 (11–18.8) | 13 (10.8–16) | 18 (16–23) | 21 (16–26) | 7.48 (7.42–7.51) | 7.45 (7.40–7.49) | 239.2 ± 47.0 * | 229.3 ± 42.0 * | 50.5 ± 53 | 50 (48–57.8) | 53 (48.8–61.3) | 85.9 ± 33.1 * | 70.9 ± 30.6 * |
| Papachatzakis et al., 2020 | 76 ± 13.4 | 78.1 ± 8.1 | 10/20 | 9/20 | 21.6 ± 8.9 | 19.6 ± 6.1 | — | — | 7.1 ± 0.1 | 7.1 ± 0.1 | 76.4 ± 28.9 | 65.2 ± 12.9 | 60.4 ± 9.9 | 62.1 ± 10.3 | 2 ± 1 | 2 ± 9 |
| Lee et al., 2018 | 73 (68–79) | 77 (71–70) | 28/44 | 29/44 | — | — | 24 (20–28) | 24 (22–29) | 7.32 ± 0.28 | 7.31 ± 0.29 | 134.8 ± 7.3 * | 134.5 ± 7.5 * | 56.4 ± 10.1 | 52.6 ± 8.8 | 7 (5–10) | 8 (6–10) |
| Sun et al., 2019 | 73.2 ± 9.0 | 70.4 ± 7.4 | 24/39 | 30/43 | 18.4 ± 2.7 | 17.3 ± 3.4 | 28.1 ± 3.3 | 27.0 ± 3.5 | 7.31 (7.29–7.33) | 7.30 (7.28–7.32) | 138.2 ± 6.6 * | 140.6 ± 6.6 * | 56 (53–62) | 59 (55–62) | 5 (4–7) | 6 (5–8) |

* distinguishes the two indicators of the variable. For example, “day” was chosen by Jing et al. (the first RCT in the table) in their study to measure the respiratory support duration, while Tan et al. (the fifth RCT in the table) prefer “hours” to be the measurement.
Likewise, two cohort studies showed a similar tendency without a significant difference. Forest plots of blood gas analysis and respiratory rate are shown in Figure 4.

3.3.3. Effect on ICU Stay. All six RCTs reported the patients’ stay in the ICU and were pooled into the analysis. The results suggested that both therapies were similar with respect to ICU stay (SMD $-0.07$, 95% CI: $-0.26$ to $0.11$). Forest plot of ICU stay is shown in Figure 5.

3.3.4. Patients’ Comfort and Complications of Therapy. Three studies [14, 15, 19] that reported patients’ comfort indicated a statistically significant effect in support of HFNC. Similarly, four studies [16, 17, 19, 20] that reported complications of therapy showed a significantly lower flatulence rate and incidence of nasal-facial breakdown rate in the HFNC group than in the NIV group (all $P < 0.05$). Besides, fewer patients in the HFNC group needed less airway care intervention. The summary of patients’ comfort and complication is shown in Table 4.

3.3.5. Heterogeneity Analysis. Significant heterogeneity was tested in PaCO$_2$ of the cohort studies ($I^2 = 87\%$, $\chi^2 = 7.52$, $P = 0.006$), but not among the RCTs ($I^2 = 30\%$, $\chi^2 = 5.73$, $P = 0.22$). There were good consistency and low heterogeneity among the other variables analyzed.

4. Discussion

The efficacy and safety of high-flow nasal cannula (HFNC) in patients with hypercapnic respiratory failure have been debatable in recent years. Pisani et al. [22] reported that COPD patients recovering from an acute exacerbation and with persistent hypercapnia showed a statistically significant response in terms of PaCO$_2$ decrease. This was strengthened...
### Intubation

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Risk ratio M-H, fixed, 95% CI |
|-------------------|---------------------|----------------|------------|-----------------------------|
| **1.1.1. RCTs**   |                     |                |            |                             |
| Jing, G., et al., 2018 | 2                  | 22             | 22         | 25.8                        | 1.00 [0.24, 4.10] |
| Papachatzakis, Y., et al., 2020 | 3                  | 36             | 36         | 12.2                        | 1.55 [0.24, 9.85] |
| Tan, D., et al., 2020 | 7                  | 44             | 42         | 28.7                        | 1.40 [0.41, 4.81] |
| Wang, J., et al., 2019 | 6                  | 23             | 42         | 21.1                        | 1.41 [0.34, 5.94] |
| Yu, Z., et al., 2019 | 3                  | 36             | 36         | 12.2                        | 1.55 [0.24, 9.85] |
| **Subtotal (95% CI)** | **161**            | **156**        | **100.0**  | **1.33 [0.68, 2.60]**       |
| **Total events** | 24                 | 18             |            |                             |

Heterogeneity: $\chi^2 = 0.56$, $df = 3$ ($P = 0.91$); $I^2 = 0$

Test for overall effect: $Z = 0.22$ ($P = 0.82$)

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Risk ratio M-H, fixed, 95% CI |
|-------------------|---------------------|----------------|------------|-----------------------------|
| **1.1.2. Cohort studies** |                     |                |            |                             |
| Lee, M.K., et al., 2018 | 11                | 44             | 44         | 58.4                        | 0.92 [0.45, 1.85] |
| Sun, J., et al., 2019 | 8                  | 39             | 43         | 41.6                        | 0.98 [0.42, 2.29] |
| **Subtotal (95% CI)** | **83**             | **87**         | **100.0**  | **0.94 [0.55, 1.62]**       |
| **Total events** | 19                 | 21             |            |                             |

Heterogeneity: $\chi^2 = 0.01$, $df = 1$ ($P = 0.91$); $I^2 = 0$

Test for overall effect: $Z = 0.21$ ($P = 0.83$)

### Mortality

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Risk ratio M-H, fixed, 95% CI |
|-------------------|---------------------|----------------|------------|-----------------------------|
| **1.1.1. RCTs**   |                     |                |            |                             |
| Jing, G., et al., 2018 | 2                  | 22             | 22         | 25.8                        | 1.00 [0.24, 4.10] |
| Papachatzakis, Y., et al., 2020 | 3                  | 36             | 36         | 12.2                        | 1.55 [0.24, 9.85] |
| Tan, D., et al., 2020 | 7                  | 44             | 42         | 28.7                        | 1.40 [0.41, 4.81] |
| Wang, J., et al., 2019 | 6                  | 23             | 42         | 21.1                        | 1.41 [0.34, 5.94] |
| Yu, Z., et al., 2019 | 3                  | 36             | 36         | 12.2                        | 1.55 [0.24, 9.85] |
| **Subtotal (95% CI)** | **161**            | **156**        | **100.0**  | **1.33 [0.68, 2.60]**       |
| **Total events** | 24                 | 18             |            |                             |

Heterogeneity: $\chi^2 = 0.22$, $df = 4$ ($P = 0.99$); $I^2 = 0$

Test for overall effect: $Z = 0.85$ ($P = 0.40$)

| Study or subgroup | Experimental Events | Control Events | Weight (%) | Risk ratio M-H, fixed, 95% CI |
|-------------------|---------------------|----------------|------------|-----------------------------|
| **1.1.2. Cohort studies** |                     |                |            |                             |
| Lee, M.K., et al., 2018 | 7                  | 44             | 44         | 58.2                        | 0.85 [0.28, 2.59] |
| Sun, J., et al., 2019 | 6                  | 39             | 43         | 41.8                        | 1.12 [0.33, 3.82] |
| **Subtotal (95% CI)** | **83**             | **87**         | **100.0**  | **0.96 [0.42, 2.20]**       |
| **Total events** | 13                 | 14             |            |                             |

Heterogeneity: $\chi^2 = 0.11$, $df = 1$ ($P = 0.74$); $I^2 = 0$

Test for overall effect: $Z = 0.09$ ($P = 0.93$)

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**Figure 3: Intubation and mortality.**

By another retrospective study among hypercapnic AECOPD patients that reported a significant treatment effect in removing CO$_2$, especially for acidic patients (baseline pH < 7.35) [23]. It was also reported that the use of HFNC resulted in dyspnea relief and hypercapnia improvement [24] and could effectively mitigate diaphragm fatigue [25]. In contrast, HFNC did not decrease PaCO$_2$ in the hypercapnic subgroup of another cross-sectional study [26] and patients with mild-to-moderate AECOPD in the trial of Yang et al. [25].

In this meta-analysis, we found that HFNC is as effective as NIV in preventing endotracheal intubation and mortality. We also found that HFNC has a similar effect as NIV on pH change, improving oxygenation, removing carbon dioxide, alleviating respiratory distress, and ICU stay. This could be attributed to the following factors. First, HFNC decrease in the dead space of the air channel improves alveolar ventilation and washes out carbon dioxide in the anatomical dead space, thereby leading to effective PaCO$_2$ reduction [27–29]. Second, HFNC decreased inhalation-expiration ratio and respiratory rate, improved breathing patterns, and subsequently reduced the work of breath [30–32]. Di Mussi et al. [33] stated that HFNC after extubation significantly decreased the neuroventilatory drive and work of breathing compared with conventional oxygen therapy. Third, by delivering high-flow gas, HFNC may produce a flow and leakage-dependent positive end-expiratory pressure (PEEP) and prevent airway collapse that may be beneficial for alveolar recruitment on the one hand and improve the mismatch between ventilation and perfusion on the other hand [34–36]. Besides, the physiological friendly gas perks up mucosal function and facilitates secretion clearance. All the factors may mitigate lung injury and induce a noninferior outcome. Given the friendly interface that would not disturb speaking, spitting, or eating and a stable flow with warm and well-humidified gas, HFNC was undoubtedly superior to NIV with regard to patients’ comfort and therapy-related complications.

Our study has several limitations. First is the fact that eligible clinical studies on the use of HFNC in hypercapnic...
respiratory failure were limited. Second is the methodological issues of the included studies, for example, explicit randomization in partial studies, lack of binding for all RCTs, and single-center design of most studies in Asia. These factors may lead to bias and weaken the strength of evidence. Besides, there was significant heterogeneity in the analysis of PaCO2 in cohort studies ($I^2 = 87\%$, $\chi^2 = 7.52$, $P = 0.006$), which was speculated to be caused by differences in the initial flow rate of HFNC and the overall severity of patients, deduced on the basis of different places from where patients were recruited. Thus, the quality of the included studies ranged from moderate to low.
### Table 4: Summary of patients’ comfort and complication.

| Study or subgroup | Nasofacial skin breakdown | Gastric and intestinal flatulence | Comfort scores | Airway care interventions |
|-------------------|---------------------------|----------------------------------|----------------|--------------------------|
| Sun et al., 2019  | 5.1% vs. 20.9%, \( P < \) 0.05 | —                                | 3.55 ± 2.01 vs. 5.15 ± 2.28, \( P = 0.02 \) | 5 (4–7) vs. 8 (7–10), \( P < 0.001 \) |
| Jing et al., 2018 | —                         | —                                | —              | —                        |
| Cong et al., 2019 | —                         | —                                | 75% vs. 57%, \( P = 0.008 \) | —                        |
| Yu et al., 2019   | —                         | 5.6% vs. 25%, \( P = 0.022 \)    | —              | —                        |
| Wang et al., 2019 | 8.7% vs. 40%, \( P = 0.028 \) | 13.0% vs. 45.0%, \( P = 0.039 \) | —              | —                        |
| Tan et al., 2020  | 0% vs. 9.6%, \( P = 0.027 \) | —                                | 7 (6–8) vs. 5 (4–7), \( P < 0.001 \) | 6 (4–7) vs. 7 (5–9.3), \( P = 0.006 \) |

### 5. Conclusion

Despite the limitations noted, HFNC may be an effective and safe alternative to prevent endotracheal intubation and mortality when NIV cannot be performed in mild-to-moderate cases of hypercapnia. Large and well-structured trials are needed to validate these findings.

### Data Availability

The studies included can be found on PubMed except two RCTs, of which one was indexed in Embase (Yu ZH et al., Academic Journal of Second Military Medical University 2019, https://doi.org/10.16781/j.0258-879x.2019.09.0989), and the other (Wang et al., Chin J Mod Med 2019, https://kns.cnki.net/kcms/detail/43.1225.R.20190613.1310.010.html) could be found on Chinese National Knowledge Infrastructure.

### Conflicts of Interest

The authors declare no conflicts of interest.

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### Supplementary Materials

This section includes Appendix 1 with detailed search terms. (Supplementary Materials)

### References

[1] D. Cook, R. Brower, J. Cooper, L. Brochard, and J.-L. Vincent, “Multicenter clinical research in adult critical care,” Critical Care Medicine, vol. 30, no. 7, pp. 1636–1643, 2002.

[2] C. Roussos and A. Koutsoukou, “Respiratory failure,” European Respiratory Journal, vol. 22, no. Supplement 47, pp. 3s–14s, 2003.

[3] A. Esteban, A. Anzueto, F. Frutos et al., “Characteristics and outcomes in adult patients receiving mechanical ventilation,” Journal of the American Medical Association, vol. 287, pp. 345–355, 2002.

[4] B. Rochwerger, L. Brochard, M. W. Elliott et al., “Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure,” European Respiratory Journal, vol. 50, no. 2, p. 1602426, 2017.

[5] F. Vagnarelli, M. Marini, G. Caretta et al., “Noninvasive ventilation: general characteristics, indications, and review of the literature,” Giornale italiano di cardiologia (Rome), vol. 18, pp. 496–504, 2017.

[6] G. Bello, G. De Pascale, and M. Antonelli, “Noninvasive ventilation,” Clinics in Chest Medicine, vol. 37, pp. 711–721, 2016.
[7] C. Crimi, A. Noto, P. Princi, A. Esquinas, and S. Nava, “A European survey of noninvasive ventilation practices,” European Respiratory Journal, vol. 36, pp. 362–369, 2010.

[8] N. Fleeman, J. Mahon, V. Bates et al., “The clinical effectiveness and cost-effectiveness of heated humidified high-flow nasal cannula compared with usual care for preterm infants: a systematic review and economic evaluation,” Health Technology Assessment, vol. 20, pp. 1–68, 2016.

[9] M. Nishimura, “High-flow nasal cannula oxygen therapy devices,” Respiratory Care, vol. 64, pp. 735–742, 2019.

[10] M. S. Stefan, P. Eckert, B. Tirimou et al., “High flow nasal oxygen therapy utilization: 7-year experience at a community teaching hospital,” Hospital Practice (1995), vol. 46, pp. 73–76, 2018.

[11] N. Ni, J. Luo, H. Yu 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?” Chest, vol. 151, pp. 764–775, 2017.

[12] J. P. T. Higgins and S. Green, Cochrane Handbook for Systematic Reviews of Interventions, The Cochrane Collaboration, London, UK, 2008, http://www.cochrane-handbook.org.

[13] G. Wells, B. Shea, D. O’Connell et al., “The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses,” 2000, http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

[14] G. Jing, J. Li, D. Hao et al., “Comparison of high flow nasal cannula with noninvasive ventilation in chronic obstructive pulmonary disease patients with hypercapnia in preventing post-extubation respiratory failure: a pilot randomized controlled trial,” Research and Nursing Health, vol. 42, pp. 217–225, 2019.

[15] L. Cong, L. Zhou, H. Liu et al., “Outcomes of high-flow nasal cannula versus non-invasive positive pressure ventilation for patients with acute exacerbations of chronic obstructive pulmonary disease,” International Journal of Clinical and Experimental Medicine, vol. 12, pp. 10863–10867, 2019.

[16] J. J. Wang, H. Y. Jiang, and Q. Li, “Randomized controlled trial,” Research and Nursing Health, vol. 42, pp. 217–225, 2019.

[17] L. Pisani, S. Betti, C. Biglia et al., “Effects of high-flow nasal cannula in patients with persistent hypercapnia after an acute COPD exacerbation: a prospective pilot study,” BioMed Central Pulmonary Medicine, vol. 20, p. 12, 2020.

[18] J. Bräunlich and H. Witz, “Nasal high-flow in acute hypercapnic exacerbation of COPD,” International Journal of Chronic Obstructive Pulmonary Disease, vol. 13, pp. 3895–3897, 2018.

[19] A. Pandya, G. Criner, J. So et al., “Tolerance and safety of humidified high-flow nasal cannula oxygen therapy in patients hospitalized with an acute exacerbation of chronic obstructive pulmonary disease (COPD),” American Journal of Respiratory and Critical Care Medicine, vol. 199, 2019.

[20] P. J. Biselli, J. P. Kirkness, L. Grote et al., “Nasal high-flow therapy reduces work of breathing compared with oxygen during sleep in COPD and smoking controls: a prospective observational study,” Journal of Applied Physiology (1985), vol. 122, pp. 82–88, 2017.

[21] S. Mckinstry, J. Pilcher, G. Bardsley et al., “Nasal high flow therapy and PtCO2 in stable COPD: a randomized cross-over trial,” Respiriology, vol. 23, no. 4, pp. 378–384, 2017.

[22] P. Biselli, K. Fricke, L. Grote et al., “Reductions in dead space ventilation with nasal high flow depend on physiological dead space volume: metabolic hood measurements during sleep in patients with COPD and controls,” European Respiratory Journal, vol. 51, 2018.

[23] C. F. Adams, P. H. Geoghegan, C. J. Spence et al., “Modelling nasal high flow therapy effects on upper airway resistance and resistive work of breathing,” Respiratory and Sleep Medicine, vol. 254, pp. 23–29, 2018.

[24] L. Pisani, L. Fasano, N. Corcione et al., “Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD,” Thorax, vol. 72, pp. 373–375, 2017.

[25] J. F. Fraser, A. J. Spooner, K. R. Dunster et al., “Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial,” Thorax, vol. 71, pp. 759–761, 2016.

[26] R. Di Mussi, S. Spadaro, T. Strippoli et al., “High-flow nasal cannula oxygen therapy decreases post-extubation neuromuscular drive and work of breathing in patients with chronic obstructive pulmonary disease,” Critical Care, vol. 22, p. 180, 2018.

[27] A. Corley, L. Caruana, A. G. Barnett et al., “Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients,” British Journal of Anaesthesia, vol. 107, pp. 998–1004, 2011.
[35] N. Groves and A. Tobin, “High flow nasal oxygen generates positive airway pressure in adult volunteers,” *Australian Critical Care*, vol. 20, pp. 126–131, 2007.

[36] J. Bräunlich, F. Mauersberger, and H. Wirtz, “Effectiveness of nasal high flow in hypercapnic COPD patients is flow and leakage dependent,” *BMC Pulmonary Medicine*, vol. 18, p. 14, 2018.