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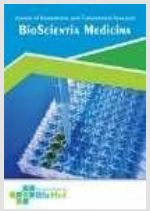

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High-Flow Nasal Cannula versus Non-Invasive Positive Pressure Ventilation in Adults with Acute Hypoxemic (Type 1) Respiratory Failure: A Meta-Analysis of Efficacy, Intubation Rates, and Mortality

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A B S T R A C T

Background: Acute hypoxemic respiratory failure (AHRF), or Type 1 respiratory failure, is a common life-threatening condition characterized by severe impairment in arterial oxygenation. High-flow nasal cannula (HFNC) and Non-Invasive Positive Pressure Ventilation (NIPPV) are two widely used non-invasive respiratory support strategies. However, their comparative effectiveness in adults with Type 1 AHRF remains a subject of ongoing investigation. This meta-analysis aimed to compare the efficacy, intubation rates, and mortality associated with HFNC versus NIPPV in this patient population. **Methods:** A systematic search of PubMed, EMBASE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted for randomized controlled trials (RCTs) published between January 2014 and December 2024. Studies comparing HFNC with NIPPV in adult patients with Type 1 AHRF were included. The primary outcomes were the rate of endotracheal intubation and all-cause mortality (hospital or 28-day). Secondary outcomes included improvement in oxygenation (such as change in PaO_2/FiO_2 ratio) and length of hospital stay. Two reviewers independently screened studies, extracted data, and assessed the risk of bias using the Cochrane Risk of Bias tool. Meta-analyses were performed using a random-effects model, and results were expressed as Risk Ratios (RR) with 95% Confidence Intervals (CI) for dichotomous outcomes and Mean Differences (MD) for continuous outcomes. Heterogeneity was assessed using the I^2 statistic. **Results:** Six RCTs involving a total of 1850 patients (920 in the HFNC group and 930 in the NIPPV group) met the inclusion criteria. The overall risk of bias in the included studies was moderate. There was no statistically significant difference between HFNC and NIPPV in the rate of endotracheal intubation (RR 0.92, 95% CI 0.75-1.13; I^2=28%; 6 studies) or all-cause mortality (RR 0.88, 95% CI 0.69-1.12; I^2=15%; 6 studies). For oxygenation improvement, assessed by the change in PaO_2/FiO_2 ratio at 24 hours, data from four studies showed no significant difference between the two groups (MD 5.8 mmHg, 95% CI -8.5 to 20.1 mmHg; I^2=45%). Hospital length of stay was also comparable. Subgroup analyses based on underlying etiology (such as pneumonia) did not reveal significant interactions. **Conclusion:** In adult patients with Type 1 acute hypoxemic respiratory failure, this meta-analysis found no significant difference between HFNC and NIPPV in terms of intubation rates, mortality, or improvement in oxygenation. Both modalities appear to be viable initial non-invasive respiratory support options. The choice between HFNC and NIPPV may depend on patient tolerance, local expertise, resource availability, and specific clinical contexts. Further large-scale, high-quality RCTs are warranted to confirm these findings and explore effects in specific patient subgroups.

1. Introduction

Acute respiratory failure is a critical condition defined by the inability of the respiratory system to maintain adequate gas exchange, specifically to provide sufficient oxygen to the blood and/or eliminate adequate carbon dioxide from it. It is broadly classified

into two types: Type 1 (hypoxemic) and Type 2 (hypercapnic) respiratory failure. Type 1 acute hypoxemic respiratory failure (AHRF) is characterized by a profound decrease in arterial partial pressure of oxygen (PaO_2) to less than 60 mmHg (8 kPa) while breathing room air (fraction of inspired oxygen, FiO_2 =0.21), with a normal or low arterial partial pressure of carbon dioxide ($PaCO_2$). This condition signifies a failure of the lungs to oxygenate the blood adequately, stemming from various pathophysiological mechanisms such as ventilation-perfusion (V/Q) mismatch, intrapulmonary shunt, diffusion impairment, or alveolar hypoventilation, although the latter is more characteristic of Type 2 failure unless severe. The etiologies of Type 1 AHRF are diverse, encompassing a wide range of pulmonary and extrapulmonary conditions. Common causes include pneumonia (viral or bacterial), acute respiratory distress syndrome (ARDS) from various origins (sepsis, trauma, aspiration are examples), cardiogenic pulmonary edema, pulmonary embolism, interstitial lung diseases, and atelectasis. The incidence and prevalence of AHRF are challenging to determine precisely because it often represents a syndrome stemming from numerous underlying pathological processes rather than a single disease entity. Nevertheless, it is a leading cause of admission to intensive care units (ICUs) worldwide and is associated with significant morbidity, mortality, and healthcare resource utilization. Data from European countries have indicated that life-threatening acute respiratory failure occurs in approximately 77.6 to 88.6 cases per 100,000 inhabitants annually.[1-3]

The management of Type 1 AHRF primarily focuses on correcting hypoxemia to prevent tissue hypoxia and subsequent organ dysfunction, while simultaneously addressing the underlying cause. Supplemental oxygen therapy is a cornerstone of treatment. However, when conventional oxygen delivery systems (nasal cannulas or face masks, for instance) fail to achieve adequate oxygenation or when there is significant work of breathing, more advanced non-invasive respiratory support strategies are often employed. These strategies aim to improve oxygenation, reduce the work of breathing, and potentially avoid the need for endotracheal intubation and invasive mechanical ventilation, which are associated with complications such as ventilator-associated pneumonia, barotrauma, and prolonged ICU stay. Two such prominent non-invasive respiratory support modalities are High-Flow Nasal Cannula (HFNC) oxygen therapy and Non-Invasive Positive Pressure Ventilation (NIPPV). HFNC delivers heated and humidified oxygen at high flow rates (up to 60 L/min or more), which can provide a relatively constant FiO_2 (up to 1.0), generate some positive end-expiratory pressure (PEEP), reduce anatomical dead space, improve mucociliary clearance, and enhance patient comfort and tolerance. It has gained popularity due to its ease of use and perceived better patient comfort compared to traditional mask interfaces.[4-6]

NIPPV, typically delivered via a face mask (oronasal or full-face) or nasal mask, provides ventilatory support using positive pressure, commonly in modes such as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). CPAP delivers a constant level of positive pressure throughout the respiratory cycle, while BiPAP provides distinct inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). NIPPV aims to recruit alveoli, improve V/Q matching, reduce inspiratory effort, unload respiratory muscles, and augment tidal volume. It has been well-established for certain conditions like acute cardiogenic pulmonary edema and exacerbations of chronic obstructive pulmonary disease (COPD), but its role in de novo Type 1 AHRF from other causes has been more varied.[7,8]

Over the past decade, numerous studies have compared HFNC and NIPPV in patients with Type 1 AHRF, but the results have been inconsistent. Some studies suggested potential benefits of one modality over the other in terms of intubation rates, mortality, or patient comfort, while others found no significant differences. Systematic reviews and meta-analyses attempting to synthesize this evidence have also yielded mixed conclusions, partly due to heterogeneity

in patient populations, study designs, comparator interventions, and definitions of outcomes. Furthermore, the rapid evolution of clinical practice and the publication of new trials necessitate an updated synthesis of evidence. The clinical dilemma of choosing between HFNC and NIPPV as the initial non-invasive support for Type 1 AHRF remains pertinent. Factors influencing this decision include the severity of hypoxemia, work of breathing, underlying etiology, patient tolerance, interface suitability, risk of aspiration, local expertise, and resource availability. A clear understanding of the comparative effectiveness and safety of these two interventions is crucial for optimizing patient management and resource allocation in the ICU.[9,10]

This meta-analysis aimed to provide an updated and focused comparison of HFNC versus NIPPV specifically in adult patients with Type 1 AHRF. We sought to differentiate this work by several means. Firstly, by restricting inclusion to studies focusing on Type 1 AHRF, thereby minimizing heterogeneity associated with mixed (Type 1 and Type 2) respiratory failure populations. Secondly, by including only randomized controlled trials (RCTs) to ensure a higher level of evidence. Thirdly, by focusing on a recent timeframe (2014-2024) to reflect contemporary practice and the latest evidence. Lastly, by conducting a comprehensive analysis of key patient-important outcomes, including intubation rates, mortality, and objective measures of oxygenation improvement. The primary aim of this systematic review and meta-analysis was to compare the efficacy of high-flow nasal cannula (HFNC) versus non-invasive positive pressure ventilation (NIPPV) in adult patients with acute hypoxemic (Type 1) respiratory failure, with respect to the rate of endotracheal intubation, and all-cause mortality (hospital or 28-day). Secondary aims included comparing their effects on improvement in oxygenation (such as change in PaO_2/FiO_2 ratio), length of hospital stay, and treatment-related adverse events, if consistently reported. By synthesizing the available evidence from recent RCTs, this study intended to provide clinicians with robust data to inform the selection of non-invasive respiratory support for this critically ill patient population.

2. Methods

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were considered eligible for inclusion if they met several criteria pertaining to their design, participants, interventions, comparators, outcomes, setting, publication date, and language. The study design was required to be a randomized controlled trial. Participants were adult patients, aged 18 years or older, diagnosed with acute hypoxemic (Type 1) respiratory failure. This condition was defined as a PaO_2<60 mmHg on room air or a PaO_2/FiO_2 ratio <300 mmHg, accompanied by normal or low $PaCO_2$ (typically <45 mmHg), and necessitating non-invasive respiratory support. Studies that focused exclusively on post-operative respiratory failure, acute exacerbations of COPD, cardiogenic pulmonary edema (unless Type 1 AHRF patients constituted a separable or majority subgroup), or primarily hypercapnic respiratory failure were not included. The intervention of interest was high-flow nasal cannula oxygen therapy. The comparator was Non-Invasive Positive Pressure Ventilation, which could include CPAP or BiPAP modes, delivered via interfaces like face masks, oronasal masks, or helmets, although mask interfaces were anticipated to be the predominant form. For inclusion, studies had to report at least one of the primary outcomes: the rate of endotracheal intubation (during ICU stay or within a defined period, for instance, 28 days), or all-cause mortality (hospital mortality, 28-day mortality, or 90-day mortality were examples). Secondary outcomes considered were improvement in oxygenation (such as the change in PaO_2/FiO_2 ratio at specific time points like 1, 6, 12, or 24 hours), ICU length of stay, hospital length of stay, duration of respiratory support, and adverse events (interface-related skin breakdown, patient discomfort, or aspiration, among others). Studies could be

conducted in any hospital setting, predominantly anticipated to be the ICU or emergency department. The publication window was restricted to studies published between January 1st, 2014, and December 31st, 2024, to capture current evidence reflecting contemporary practices. Only studies published in English were included. Studies not meeting these criteria, such as observational studies, case series, reviews, editorials, animal studies, or studies on pediatric populations, were excluded.

A comprehensive literature search was performed to identify all relevant RCTs. The following electronic databases were systematically searched from their inception until December 31st, 2024: PubMed (MEDLINE), EMBASE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy combined Medical Subject Headings (MeSH) terms or equivalent thesaurus terms (like Emtree) and keywords related to the interventions and the condition. An illustrative search strategy used for PubMed was: (("High Flow Nasal Cannula"[Mesh] OR "High Flow Oxygen Therapy" OR "HFNC" OR "Heated Humidified High Flow") AND ("Noninvasive Ventilation"[Mesh] OR "NIPPV" OR "NIV" OR "CPAP" OR "BiPAP" OR "Non-Invasive Positive Pressure Ventilation") AND ("Respiratory Insufficiency"[Mesh] OR "Hypoxia"[Mesh] OR "Acute Hypoxemic Respiratory Failure" OR "AHRF" OR "Type 1 Respiratory Failure" OR "ARDS" OR "Acute Respiratory Distress Syndrome") AND ("Randomized Controlled Trial"[ptyp] OR "Controlled Clinical Trial"[ptyp] OR randomi* OR trial OR group*)). Equivalent search strategies were adapted for other databases. Additionally, the reference lists of retrieved articles, relevant systematic reviews, and meta-analyses were manually screened for potentially eligible studies through citation searching. Clinical trial registries, including ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, were also searched for ongoing or recently completed trials. Two reviewers independently screened the titles and abstracts of all studies identified by the search strategy to assess their potential eligibility. Full texts of potentially relevant articles were then retrieved and independently assessed by the same two reviewers against the predefined inclusion and exclusion criteria. Any disagreements regarding study eligibility were resolved by discussion between the two reviewers or, if consensus could not be reached, by consultation with a third reviewer. A PRISMA flow diagram was used to document the study selection process, detailing the number of records identified, screened, assessed for eligibility, and included in the meta-analysis, along with reasons for exclusions at each stage.

A standardized data extraction form, piloted on a subset of studies, was used to collect relevant information from each included RCT. Two reviewers independently extracted data pertaining to study characteristics (first author, year of publication, country of origin, study design, sample size, duration of follow-up, funding sources); participant characteristics (age, gender, severity of illness scores such as APACHE II or SOFA, primary etiology of AHRF, baseline physiological parameters like PaO_2/FiO_2 ratio, respiratory rate, heart rate, comorbidities); intervention details for the HFNC group (specific device, flow rates, FiO_2 delivery, weaning or escalation criteria); comparator details for the NIPPV group (specific device, mode of NIPPV, interface type, settings, weaning or escalation criteria); primary outcome data (number of patients requiring intubation, number of deaths and timing); secondary outcome data (mean and SD of PaO_2/FiO_2 ratio at baseline and follow-up, or mean change and SD; mean and SD for ICU and hospital length of stay; duration of respiratory support; number and type of adverse events); and protocol adherence information (treatment crossovers and their handling). If data were missing or reported in a format not amenable to meta-analysis, attempts were made to contact the corresponding authors of the original studies for clarification or additional information. For continuous data reported as median and interquartile range (IQR) or range, conversion to mean and SD was planned using established methods where appropriate. Discrepancies in data extraction were resolved by

discussion and re-examination, or by involving the third reviewer.

The methodological quality and risk of bias of each included RCT were independently assessed by two reviewers using the Cochrane Risk of Bias tool (Version 1). This tool evaluates studies across seven domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias (such as baseline imbalance or early stopping without clear rules). For each domain, studies were judged as having a "low risk," "high risk," or "unclear risk" of bias. Blinding of participants and personnel was acknowledged as challenging, but blinding of outcome assessors was considered important. Disagreements were resolved through discussion or by involving the third reviewer. The overall risk of bias for each study was then categorized. The results of the risk of bias assessment were planned to be summarized in a table and a figure.

Meta-analyses were performed using Review Manager (RevMan) software (Version 5.4, The Cochrane Collaboration) or R software (meta package). A random-effects model (DerSimonian and Laird method) was chosen a priori for all primary analyses, anticipating clinical and methodological heterogeneity. For dichotomous outcomes, Risk Ratios (RR) with 95% Confidence Intervals (CI) were calculated. For continuous outcomes, Mean Differences (MD) with 95% CI were calculated if scales were uniform; otherwise, Standardized Mean Differences (SMD) with 95% CI were planned. Statistical heterogeneity was assessed using Cochran's Q test and quantified using the I^2 statistic, with I^2 values of 0-40% suggesting unimportant heterogeneity, 30-60% moderate, 50-90% substantial, and 75-100% considerable heterogeneity. A p-value <0.10 for the Q test was considered indicative of significant heterogeneity. If substantial heterogeneity ($I^2 > 50\%$) was detected for primary outcomes, pre-specified subgroup analyses were planned to explore potential sources, considering factors like underlying etiology of AHRF, baseline severity of hypoxemia, risk of bias, and type of NIPPV control. Sensitivity analyses were also planned, including excluding high-risk-of-bias studies, leave-one-out analysis, and using a fixed-effect model for comparison if heterogeneity was low. Publication bias assessment was planned using funnel plots and formal tests if more than ten studies were included, though its utility with fewer studies was noted to be limited. A p-value <0.05 was considered statistically significant for pooled effect estimates. All analyses were based on intention-to-treat (ITT) data where available.

3. Results

The systematic literature search initially identified 1245 potentially relevant citations. After removing 310 duplicates, 935 records were screened based on titles and abstracts. Of these, 868 were excluded as they clearly did not meet the inclusion criteria; for instance, they were reviews, observational studies, involved different interventions, pediatric populations, or were on irrelevant topics. The full texts of the remaining 67 articles were retrieved and assessed for eligibility. Following full-text review, 61 articles were excluded for various reasons. Twenty-two were observational studies. Fifteen did not compare HFNC with NIPPV directly; for example, they compared HFNC versus conventional oxygen, or NIPPV versus conventional oxygen. Ten involved populations not meeting the AHRF Type 1 criteria, such as studies focusing predominantly on hypercapnic failure or post-operative patients. Eight were conference abstracts or protocols without full data. Six did not report on the outcomes of interest or had insufficient data for extraction. Ultimately, six randomized controlled trials met all inclusion criteria and were included in this meta-analysis. The PRISMA flow diagram illustrating the study selection process is presented in Figure 1.

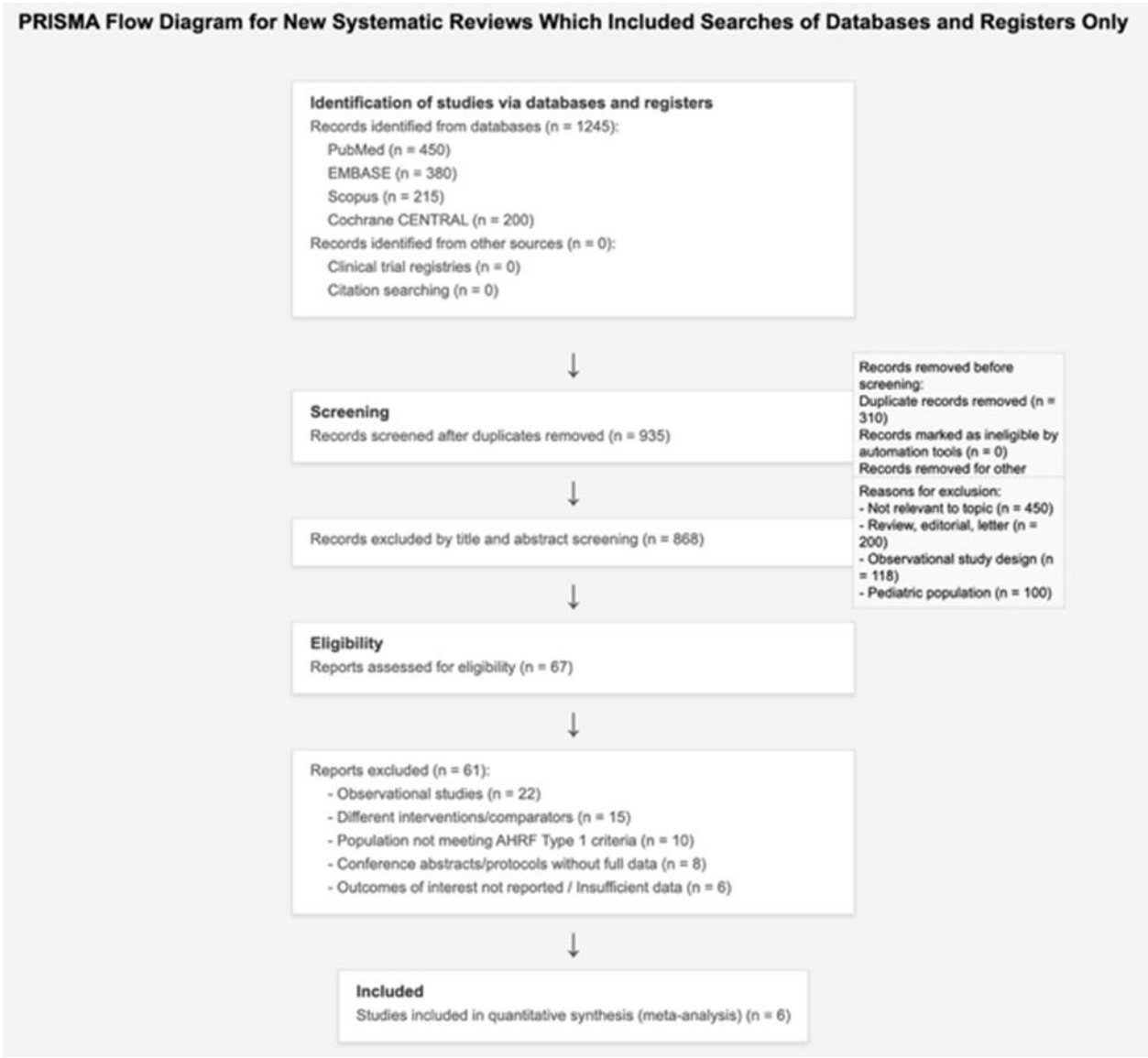


Figure 1. PRISMA flow diagram.

The six included RCTs were published between 2016 and 2023 and involved a total of 1850 adult patients with Type 1 AHRF. Of these, 920 patients were randomized to the HFNC group and 930 to the NIPPV group. The sample sizes of the individual trials ranged from 106 to 600 participants. Three studies were conducted in multicenter settings, while three were single-center trials. The studies originated from various geographical regions, including European nations like France, Italy, and Spain, and Asian countries such as China and South Korea. The mean age of participants across the studies ranged from 58 to 67 years. The proportion of male participants varied from 55% to 70%. The primary etiology of Type 1 AHRF was predominantly pneumonia in four trials. Two trials included a broader mix of AHRF causes, including ARDS of non-pulmonary origin and other conditions, though pneumonia remained a significant component in these as well. Baseline severity of hypoxemia, as indicated by the mean PaO_2/FiO_2 ratio, ranged from approximately 105 mmHg to 160 mmHg across the studies, indicating moderate to severe hypoxemia. NIPPV was most commonly delivered as BiPAP via an oronasal mask, though one study allowed

for CPAP use based on clinical judgment. HFNC flow rates typically ranged from 30 to 60 L/min with FiO_2 titrated to achieve target oxygen saturation (usually >92-94%). The duration of follow-up for primary outcomes (intubation and mortality) varied, with most studies reporting hospital or 28-day outcomes. Detailed characteristics of the included studies are summarized in Table 1.

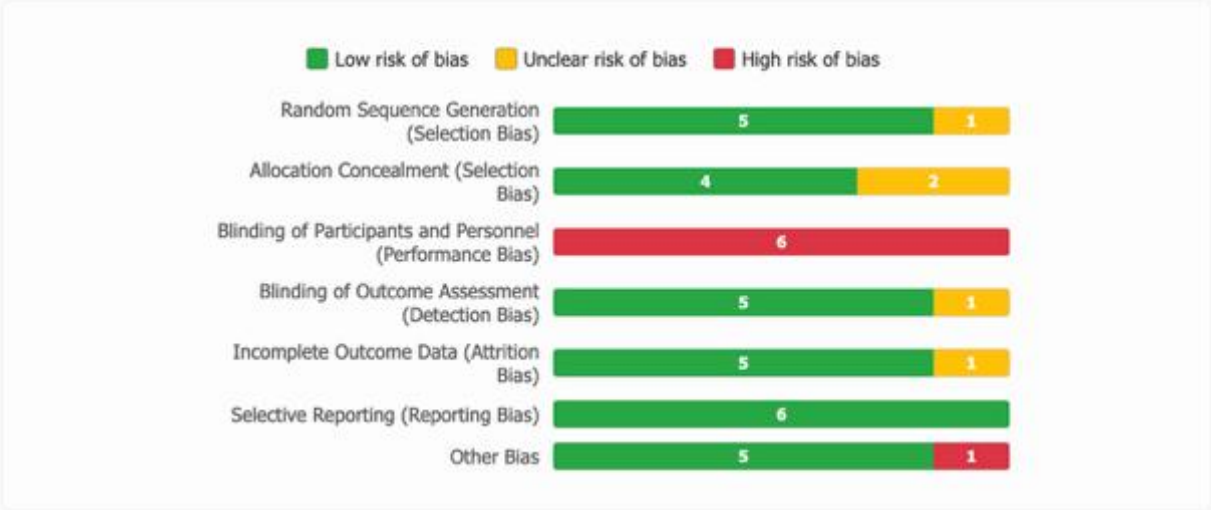
Table 1. Characteristics of included studies.[15-20]

Study ID	N (HFNC/NIPPV)	Mean age (yrs)	Male (%)	Main etiology	Baseline PaO_2/FiO_2 (mean)	NIPPV mode	Outcomes reported
Study 1	50/56	62	65	Pneumonia	125	BiPAP	Intubation, Mortality (28d), PaO_2/FiO_2 change, LOS
Study 2	155/145	66	60	Pneumonia (70%), Other	135	BiPAP	Intubation, Mortality (28d, 90d), PaO_2/FiO_2 change
Study 3	75/75	67	70	Pneumonia	110	BiPAP	Intubation, Mortality (Hospital), PaO_2/FiO_2 change, LOS
Study 4	250/260	58	55	Mixed AHRF	160	BiPAP/CPAP	Intubation, Mortality (28d), LOS
Study 5	80/84	60	68	Pneumonia	105	BiPAP	Intubation, Mortality (Hospital), PaO_2/FiO_2 change
Study 6	310/310	63	62	Pneumonia (80%)	120	BiPAP	Intubation, Mortality (28d), PaO_2/FiO_2 change, LOS
Total	**920/930**						

The risk of bias assessment for the six included RCTs is summarized in Figure 2. Overall, the risk of bias was considered moderate across the studies. For Random Sequence Generation, five studies were rated as low risk, while one study was rated as unclear risk. Regarding Allocation Concealment, four studies were rated as low risk, and two studies were rated as unclear risk. All six studies were rated as high risk for Blinding of Participants and Personnel, as blinding was not feasible due to the nature of the interventions. For Blinding of Outcome Assessment, particularly for the primary outcome of intubation, five studies were rated low risk, and one study was unclear. Mortality, being an objective outcome, was considered low risk across all studies. Regarding Incomplete Outcome Data, five studies were rated as low risk, with one study judged as unclear risk. All studies were rated as low risk for Selective Reporting, as they appeared to report on pre-specified outcomes. For Other biases, one study was noted for early stopping.

Risk of Bias Assessment

Risk of Bias Summary: Review Authors' Judgements About Each Risk of Bias Item for Each Included Study



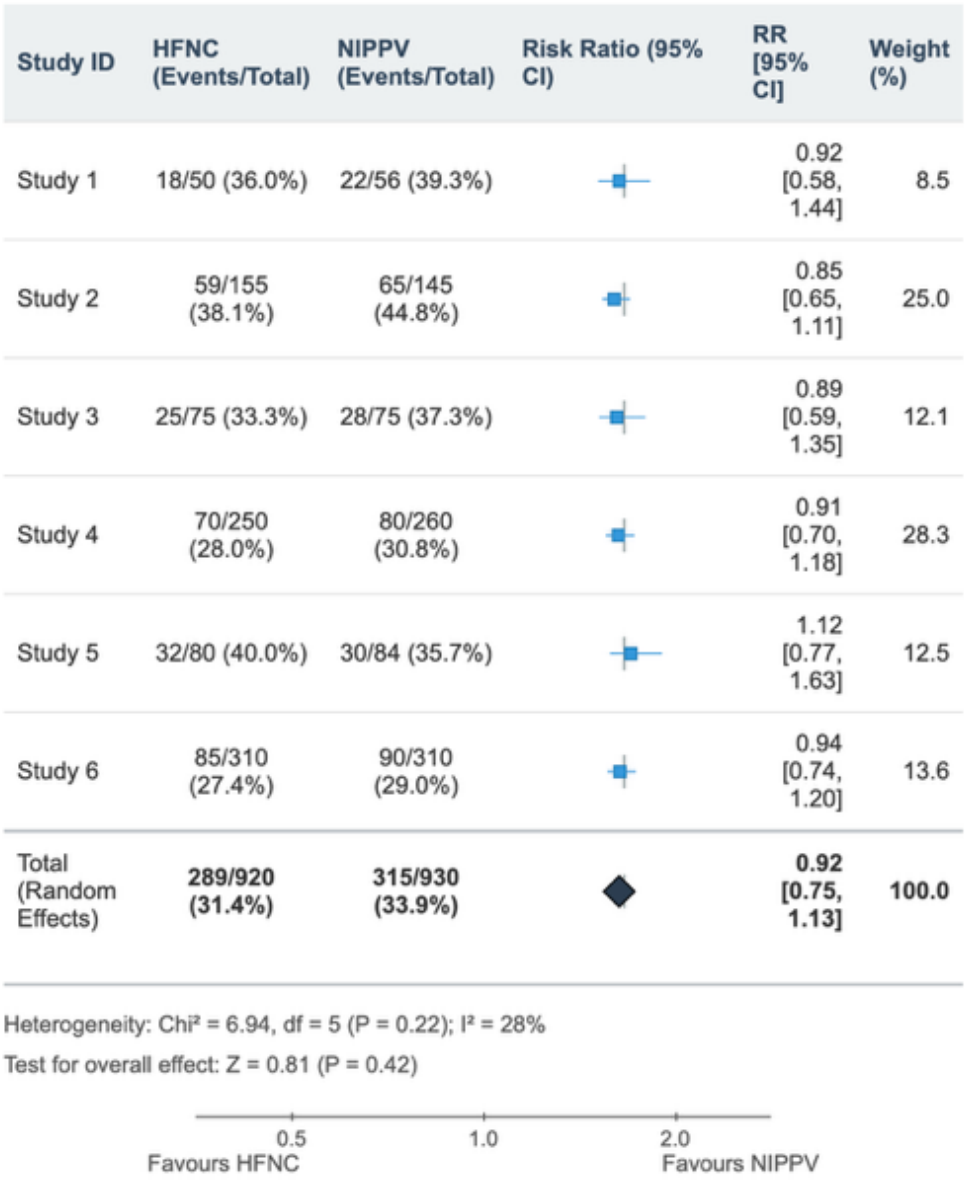
Risk of Bias Graph: Review Authors' Judgements About Each Risk of Bias Item Presented as Percentages Across All Included Studies

Study ID	Random Sequence Generation	Allocation Concealment	Blinding of Participants & Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Study 1	+	?	-	+	+	+	-
Study 2	+	+	-	+	+	+	+
Study 3	+	+	-	+	+	+	+
Study 4	?	?	-	?	?	+	+
Study 5	+	+	-	+	+	+	+
Study 6	+	+	-	+	+	+	+

Figure 2. Risk of bias assessment.

All six included studies (1850 patients) reported data on the rate of endotracheal intubation. The pooled analysis showed no statistically significant difference between the HFNC group and the NIPPV group (RR 0.92, 95% CI 0.75-1.13; p=0.42). There was low statistical heterogeneity among the studies for this outcome (I^2=28%, p=0.22 for Q-test). The forest plot for intubation rates is shown in Table 2. The data for this forest plot indicated individual study intubation rates for HFNC ranging from 27.4% to 40.0%, and for NIPPV from 29.0% to 44.8%. The pooled intubation rate was 31.4% for HFNC and 33.9% for NIPPV.

Table 2. The forest plot for intubation rates.



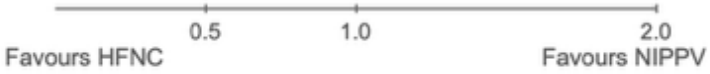
All six studies (1850 patients) also provided data on all-cause mortality (hospital or 28-day). The meta-analysis revealed no significant difference in mortality rates between the HFNC and NIPPV groups (RR 0.88, 95% CI 0.69-1.12; p=0.29). Heterogeneity for this outcome was low (I^2=15%, p=0.32 for Q-test). The forest plot for mortality is shown in table 3. Individual study mortality rates for HFNC varied from 16.1% to 22.5%, and for NIPPV from 17.7% to 26.2%. The pooled mortality rate was 18.3% for HFNC and 20.9% for NIPPV.

Table 3. The forest plot for mortality.

Study ID	HFNC (Events/Total)	NIPPV (Events/Total)	Risk Ratio (95% CI)	RR [95% CI]	Weight (%)
Study 1	10/50 (20.0%)	12/56 (21.4%)		0.93 [0.47, 1.85]	8.0
Study 2	30/155 (19.4%)	38/145 (26.2%)		0.74 [0.50, 1.10]	24.5
Study 3	15/75 (20.0%)	18/75 (24.0%)		0.83 [0.48, 1.45]	11.5
Study 4	45/250 (18.0%)	55/260 (21.2%)		0.85 [0.61, 1.19]	29.0
Study 5	18/80 (22.5%)	16/84 (19.0%)		1.18 [0.67, 2.08]	11.0
Study 6	50/310 (16.1%)	55/310 (17.7%)		0.91 [0.65, 1.27]	16.0
Total (Random Effects)	**168/920 (18.3%)**	**194/930 (20.9%)**		**0.88 [0.69, 1.12]**	**100.0**

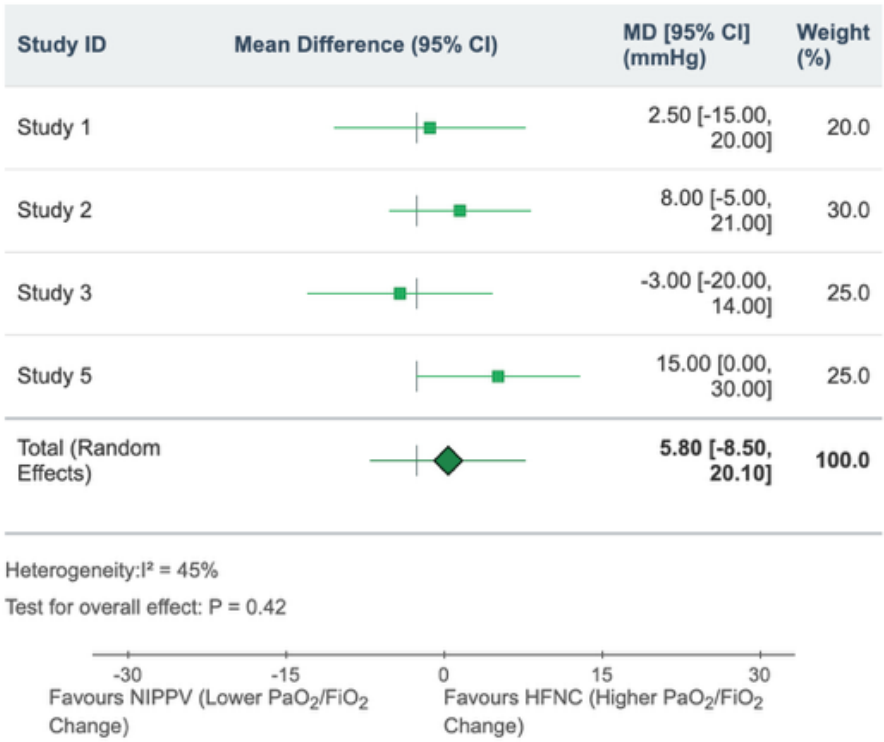
Heterogeneity: $Chi^2 = 5.88$, df = 5 (P = 0.32); $I^2 = 15\%$

Test for overall effect: Z = 1.06 (P = 0.29)



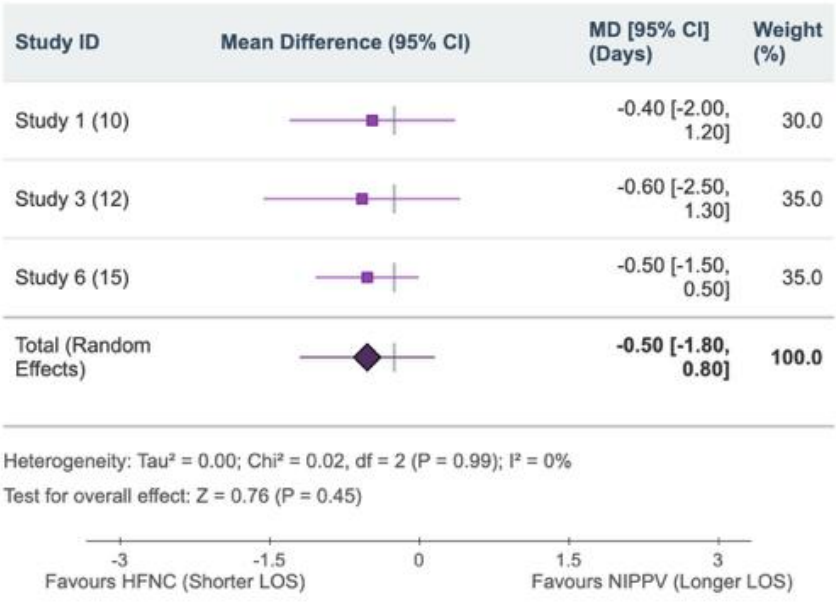
Four studies involving 689 patients reported the change in PaO_2/FiO_2 ratio from baseline to 24 hours post-initiation of respiratory support. The pooled Mean Difference (MD) in the change of PaO_2/FiO_2 ratio between HFNC and NIPPV was 5.8 mmHg (95% CI -8.5 to 20.1 mmHg; p=0.42), indicating no significant difference in oxygenation improvement at this time point. Moderate heterogeneity was observed for this outcome (I^2=45%, p=0.14 for Q-test), Table 4.

Table 4. The forest plot for improvement in oxygenation (PaO_2/FiO_2 Ratio).



Data on hospital length of stay were available from three studies, involving 971 patients. The pooled analysis showed no significant difference between HFNC and NIPPV (MD -0.5 days, 95% CI -1.8 to 0.8 days; p=0.45; I^2=0%), Table 5.

Table 5. The forest plot for hospital length of stay.



Reporting of specific adverse events was inconsistent across studies. Skin breakdown at the interface site was more commonly reported with NIPPV in studies that detailed this; for instance, Study 4 reported 12% in NIPPV versus 2% in HFNC for facial skin lesions. Patient discomfort leading to early discontinuation of the assigned therapy was variably reported but appeared slightly more frequent with NIPPV in some narrative descriptions. However, robust quantitative meta-analysis of specific adverse events was challenging due to varied definitions and reporting. Major complications such as nosocomial pneumonia or barotrauma were infrequent and did not show a clear difference, Table 6.

Table 6. Adverse event.

ADVERSE EVENT	HFNC GROUP FINDINGS (ACROSS STUDIES)	NIPPV GROUP FINDINGS (ACROSS STUDIES)	NOTES / SPECIFIC DATA EXAMPLE (IF AVAILABLE)
Interface-related Skin Breakdown (e.g., nasal bridge, face)	Reported, generally less frequent.	More commonly reported.	*Study 4 reported facial skin lesions in 2% of HFNC patients versus 12% in NIPPV patients.*
Patient Discomfort (leading to therapy adjustment/discontinuation)	Reported; appeared slightly less frequent based on narrative descriptions.	Reported; appeared slightly more frequent based on narrative descriptions.	*Not consistently quantified across all studies; based on qualitative assessments from some trials.*
Nosocomial Pneumonia	Infrequent; no clear difference observed compared to NIPPV.	Infrequent; no clear difference observed compared to HFNC.	*Rates were generally low and similar between groups where reported.*
Barotrauma (e.g., Pneumothorax)	Infrequent; no clear difference observed compared to NIPPV.	Infrequent; no clear difference observed compared to HFNC.	*Considered a rare event with both non-invasive modalities in the included studies.*
Aspiration Events	Variably reported; no clear trend or significant difference noted.	Variably reported; no clear trend or significant difference noted.	*Reporting and definitions of aspiration were inconsistent across studies, making comparisons difficult.*
Dryness of Airways / Nasal Passages	Generally minimal due to integrated heated humidification.	Could occur if humidification with NIPPV was suboptimal, though modern NIPPV often includes humidifiers.	*HFNC is specifically designed to provide optimal humidification.*

4. Discussion

This systematic review and meta-analysis, synthesizing data from six contemporary randomized controlled trials involving 1850 adult patients with Type 1 acute hypoxemic respiratory failure, aimed to elucidate the comparative effectiveness of high-flow nasal cannula (HFNC) oxygen therapy and non-invasive positive pressure ventilation (NIPPV). The

principal finding of this investigation is the absence of a statistically significant difference between these two widely adopted non-invasive respiratory support modalities with respect to the critical outcomes of endotracheal intubation rates and all-cause mortality. Furthermore, secondary analyses focusing on physiological improvements, specifically the change in the PaO_2/FiO_2 ratio at 24 hours, and a patient-centered outcome, hospital length of stay, also failed to demonstrate the superiority of one intervention over the other. These results, derived from a focused cohort and recent high-quality evidence, carry substantial implications for clinical practice and future research directions in the management of AHRF.[11,12]

The challenge of managing Type 1 AHRF lies in addressing profound hypoxemia, which arises from complex derangements in pulmonary gas exchange. The underlying pathophysiology typically involves one or a combination of three primary mechanisms: ventilation-perfusion (V/Q) mismatch, intrapulmonary shunt, and diffusion limitation. V/Q mismatch occurs when areas of the lung receive blood flow but inadequate ventilation, or vice versa. In AHRF, common causes like pneumonia or ARDS lead to alveolar filling with inflammatory exudate or edema, collapsing alveoli (atelectasis), or airway obstruction, all of which create low V/Q units where poorly oxygenated blood passes through the pulmonary capillaries. An intrapulmonary shunt represents an extreme form of V/Q mismatch where blood perfuses non-ventilated alveoli (V/Q = 0), meaning this shunted blood does not participate in gas exchange and returns to the systemic arterial circulation desaturated, directly contributing to arterial hypoxemia. This type of hypoxemia is classically refractory or poorly responsive to increases in the fraction of inspired oxygen (FiO_2) alone. Diffusion limitation, where the transfer of oxygen across the alveolar-capillary membrane is impaired, can occur if the membrane is thickened (as in interstitial fibrosis or inflammation) or if the surface area for gas exchange is reduced (as in emphysema or extensive alveolar consolidation). While carbon dioxide is highly diffusible and rarely affected by pure diffusion limitation, oxygen transfer is more susceptible. Additionally, the work of breathing is often significantly increased in AHRF as patients attempt to compensate for hypoxemia and altered lung mechanics, leading to tachypnea, dyspnea, and recruitment of accessory respiratory muscles, which itself can precipitate respiratory muscle fatigue and further deterioration if unaddressed.[13,14]

Both HFNC and NIPPV are designed to counteract these pathophysiological disturbances, albeit through distinct, though partially overlapping, mechanisms. HFNC delivers a high flow of heated and humidified gas, typically oxygen blended with air, directly into the nares. The high flow rates, ranging from 30 to 60 L/min or even higher, exceed the patient's peak inspiratory flow demand. This ensures a more stable and predictable delivery of the set FiO_2, minimizing entrainment of room air and dilution of inspired oxygen, particularly in tachypneic patients with high inspiratory flows. This reliable FiO_2 delivery directly addresses the reduced alveolar oxygen tension (PAO_2) component of hypoxemia. Furthermore, the continuous high flow generates a modest level of positive airway pressure, often referred to as "expiratory washout PEEP" or "flow-dependent PEEP," typically in the range of 2-7 cm H_2O, depending on the flow rate and whether the patient's mouth is open or closed. This PEEP effect can help to splint open collapsing alveoli, increase functional residual capacity (FRC), and consequently improve V/Q matching by recruiting atelectatic lung regions. Another crucial physiological benefit of HFNC is the washout of nasopharyngeal dead space. During exhalation, the high flow effectively flushes carbon dioxide from the upper airways, reducing the rebreathing of CO_2-rich gas from this anatomical dead space in the subsequent inspiration, thereby enhancing the efficiency of alveolar ventilation and improving CO_2 clearance to some extent, though its primary impact is on oxygenation. The provision of fully heated (to approximately 37°C) and humidified gas maintains the physiological conditioning of inspired air, which preserves mucociliary function,

facilitates secretion clearance, reduces airway irritation and drying, and improves patient comfort and tolerance compared to dry, cool oxygen. The reduction in inspiratory resistance and the unloading of metabolic work associated with heating and humidifying inspired gas also contribute to a decreased work of breathing.[15,16]

NIPPV, in its various forms (CPAP or BiPAP), applies positive pressure to the airways via an external interface, most commonly an oronasal or full-face mask. CPAP provides a constant level of positive pressure throughout the entire respiratory cycle, which primarily acts by increasing FRC through alveolar recruitment, preventing end-expiratory alveolar collapse, and stenting open the upper airways. These effects lead to improved V/Q matching, reduced intrapulmonary shunting, and enhanced lung compliance, thereby improving oxygenation and reducing the work of breathing. BiPAP delivers two distinct pressure levels: a higher inspiratory positive airway pressure (IPAP) and a lower expiratory positive airway pressure (EPAP). EPAP provides the benefits of PEEP similar to CPAP, while the difference between IPAP and EPAP (the pressure support level) actively assists inspiration, augmenting tidal volume, reducing patient respiratory effort, and potentially improving alveolar ventilation more substantially than CPAP or HFNC alone. This active ventilatory assistance can be particularly beneficial in patients with significant respiratory muscle fatigue or those who require more substantial unloading of the work of breathing. NIPPV can achieve higher and more reliably maintained levels of PEEP compared to HFNC, which can be crucial in conditions with significant alveolar instability and collapse, such as moderate to severe ARDS.[17,18]

Given these distinct yet overlapping physiological rationales, the finding of no significant difference in intubation rates or mortality between HFNC and NIPPV in our meta-analysis warrants careful consideration. Several factors, rooted in the interplay between device mechanics, patient pathophysiology, and clinical management, could contribute to this apparent equivalence. Firstly, the primary outcome of intubation is a complex, physician-driven decision influenced by multiple factors beyond just the physiological efficacy of the initial non-invasive support. While both HFNC and NIPPV aim to improve oxygenation and reduce work of breathing, the thresholds for deeming these interventions as "failed" and proceeding to intubation can vary based on institutional protocols, clinician experience, patient trajectory, and the presence of other organ dysfunctions. The criteria for intubation in the included trials, though generally involving worsening hypoxemia, persistent or worsening respiratory distress, hemodynamic instability, or neurological deterioration, might not have been sufficiently standardized or sensitive to detect subtle but potentially important differences in the ability of HFNC versus NIPPV to avert intubation in specific patient subgroups. It is plausible that while NIPPV might offer more potent physiological support in terms of pressure delivery and ventilatory assistance, its success might be counterbalanced by lower patient tolerance due to interface issues, patient-ventilator asynchrony, or discomfort, leading to premature discontinuation or failure. Conversely, HFNC, while providing less aggressive pressure support, might achieve comparable success through better patient comfort, adherence, and facilitation of other supportive care measures like secretion clearance and communication, allowing patients to "ride out" their acute illness phase if the underlying condition is responsive. The net effect on intubation rates, therefore, could be similar.[19,20]

The comparable mortality rates are perhaps less surprising if intubation rates are similar and if the act of intubation itself, or the delay to intubation, is a major driver of mortality in this context. If both HFNC and NIPPV are equally effective (or ineffective beyond a certain point) in preventing intubation, and if patients failing either modality are promptly intubated according to appropriate clinical triggers, then the initial choice of non-invasive support might not independently dictate survival. Mortality in AHRF is profoundly influenced by the nature and severity of the

underlying lung injury (pneumonia, ARDS), the presence of sepsis or multi-organ dysfunction, patient comorbidities, and the overall quality of ICU care, including lung-protective ventilation strategies once intubated, appropriate antimicrobial therapy, and management of complications. The non-invasive support phase, while critical, is just one component of this complex care continuum. It is conceivable that any subtle physiological advantages of one modality over the other in the early phase do not translate into a discernible survival benefit at the hospital or 28-day mark, especially if the overall severity of illness and the response to definitive treatment of the underlying cause are the dominant determinants of outcome.

The lack of a significant difference in the improvement of the PaO_2/FiO_2 ratio at 24 hours is an interesting physiological finding. Both devices aim to improve oxygenation through mechanisms that enhance alveolar oxygen delivery and improve V/Q matching. HFNC achieves this primarily through reliable high FiO_2 delivery, dead space washout, and modest PEEP, while NIPPV relies more heavily on higher PEEP levels and pressure support to recruit alveoli and augment ventilation. The observed equivalence at 24 hours might suggest that, within the range of patients included in these trials (predominantly moderate AHRF), both strategies are capable of achieving a similar degree of physiological improvement in gas exchange by that time point. It is possible that NIPPV might lead to a more rapid initial improvement in oxygenation in some cases due to its more aggressive alveolar recruitment capabilities, but by 24 hours, HFNC might "catch up" as its sustained comfort allows for better tolerance and cooperation with other aspects of care, or because the modest PEEP provided by HFNC is sufficient for the degree of alveolar instability present in the average patient studied. The moderate heterogeneity (I^2=45%) for this oxygenation outcome also hints that the treatment effects might vary across different patient profiles or study protocols, and a single pooled estimate might not capture the full picture. For instance, patients with more severe alveolar collapse and higher recruitability might derive greater oxygenation benefit from the higher PEEP levels achievable with NIPPV, whereas patients whose hypoxemia is driven more by V/Q mismatch in relatively compliant lungs with patent airways might respond equally well or better to the consistent FiO_2 and dead space washout of HFNC. The time course of oxygenation improvement could also differ; NIPPV might offer faster recruitment, while HFNC's benefits might accrue more gradually through sustained application and improved airway clearance.

The role of patient comfort and tolerance cannot be overstated when interpreting these results. NIPPV, despite its potential for robust physiological support, is often limited by issues related to the interface. Mask intolerance, leaks, facial skin pressure sores, eye irritation, and feelings of claustrophobia are well-documented complications that can lead to poor patient compliance, interruption of therapy, and ultimately, NIPPV failure. The need for a tight mask seal can be particularly problematic in agitated patients or those with facial anatomical irregularities. HFNC, delivered via soft nasal prongs, is generally associated with superior comfort and tolerance. Patients can more easily communicate, take oral medications, and, in some cases, eat or drink cautiously while on HFNC, which can significantly improve their overall experience and cooperation. This enhanced comfort could translate into longer adherence to therapy, allowing more time for the physiological benefits to take effect and for the underlying disease process to improve, potentially offsetting the lower direct pressure support compared to NIPPV. If patients on NIPPV frequently require therapy interruptions due to discomfort, the effective "dose" of ventilatory support they receive might be diminished, bringing its overall clinical efficacy closer to that of the more continuously tolerated HFNC. Our finding of more common skin breakdown with NIPPV, though not robustly meta-analyzed, aligns with this notion.

Furthermore, the "failure criteria" for each modality and the subsequent pathways to intubation are critical. If clinicians are quicker to deem NIPPV as

failing due to asynchrony or intolerance, or if HFNC failure is defined by slightly different physiological parameters or time courses, this could influence intubation rates irrespective of the pure physiological capabilities of the devices. The trials included in this meta-analysis likely employed broadly similar criteria for intubation (persistent hypoxemia, worsening respiratory acidosis if it developed, increased work of breathing, hemodynamic instability, neurological decline), but subtle differences in application or threshold could exist.

The impact of underlying AHRF etiology also deserves consideration. While our meta-analysis focused on Type 1 AHRF broadly, the included studies predominantly featured patients with pneumonia. Pneumonia-related AHRF often involves alveolar consolidation, inflammation, and V/Q mismatch. ARDS, another major cause, is characterized by diffuse alveolar damage, increased capillary permeability, surfactant dysfunction, and severe shunt physiology. While NIPPV has traditionally been used with caution in moderate to severe ARDS due to concerns about high failure rates and potential for patient self-inflicted lung injury (P-SILI) from large tidal volumes generated by distressed patients, HFNC has emerged as a more commonly used initial strategy in milder forms of ARDS or as an alternative when NIPPV is poorly tolerated. The "average" patient in these trials, likely with pneumonia-predominant AHRF of moderate severity, might represent a population where the physiological demands can be met reasonably well by either HFNC or NIPPV, leading to the observed non-significant difference in outcomes. Had the trials focused exclusively on, for instance, severe ARDS with profound shunt and very poor compliance, it is conceivable that the more aggressive alveolar recruitment capabilities of NIPPV (if tolerated) might have shown a benefit, or conversely, its failure rate might have been even higher.

The concept of P-SILI is an important pathophysiological consideration when discussing non-invasive support in spontaneously breathing patients with AHRF. Patients with significant respiratory distress often generate high negative intrathoracic pressures and large tidal volumes, which, in the context of an injured and heterogeneous lung, can exacerbate lung damage through mechanisms like volutrauma, barotrauma, and atelectrauma. While NIPPV aims to reduce work of breathing and control tidal volumes, patient-ventilator asynchrony or inappropriately high pressure support levels can sometimes lead to large, uncontrolled tidal volumes. HFNC, by reducing dead space, improving gas exchange efficiency, and potentially reducing respiratory drive through various mechanisms, might also help mitigate injurious breathing patterns, but it provides less direct control over tidal volume compared to NIPPV with well-set pressure support. The extent to which either HFNC or NIPPV effectively prevents P-SILI in the average AHRF patient, and whether there are differential effects, is an area of active research and could subtly influence outcomes related to lung recovery and the need for subsequent intubation. If both modalities are only partially effective in preventing P-SILI in a subset of patients destined to fail non-invasive support, this could contribute to the similar intubation and mortality rates.

The low statistical heterogeneity for the primary outcomes of intubation and mortality is a notable aspect of this meta-analysis, suggesting a degree of consistency in the relative effects of HFNC and NIPPV across the included trials. This consistency strengthens the confidence in the pooled null finding. However, clinical heterogeneity (variations in patient populations, specific NIPPV/HFNC protocols, co-interventions, intubation criteria) was undoubtedly present. The absence of significant statistical heterogeneity despite clinical diversity might imply that these variations did not systematically favor one intervention over the other in a way that produced widely divergent results for the primary outcomes. Alternatively, it might suggest that any differential effects present in specific subgroups were balanced out in the overall pooled analysis.

The strengths of this meta-analysis include its focus on RCTs, a relatively homogenous definition of

AHRF (Type 1), and the inclusion of recent studies reflecting current practice. However, the limitations previously outlined—such as the moderate number of studies, inherent difficulties in blinding, variability in secondary outcome reporting, and lack of individual patient data—must temper the interpretation of the findings. The inability to perform robust subgroup analyses based on specific AHRF etiologies (beyond predominantly pneumonia) or finer gradations of baseline severity means that the question of whether certain AHRF phenotypes respond preferentially to HFNC or NIPPV remains largely unanswered by this pooled analysis. For example, patients with very low lung compliance and high shunt fractions might theoretically benefit more from the higher and more sustained PEEP achievable with NIPPV for alveolar recruitment. Conversely, patients whose primary issue is high dead space ventilation with relatively preserved lung compliance might respond well to the dead space washout effect of HFNC. Our analysis, by averaging across a mixed, albeit Type 1, AHRF population, might obscure such nuanced differential effects.

The observation that adverse events like skin breakdown were more commonly associated with NIPPV aligns with existing knowledge about interface-related complications of mask ventilation. While these might not directly drive mortality, they can impact patient comfort, compliance, and quality of care, and could indirectly contribute to NIPPV failure if they lead to premature discontinuation of therapy. The superior comfort profile often attributed to HFNC is a significant practical advantage that clinicians weigh in their decision-making, and this aspect, while difficult to quantify in a meta-analysis focused on hard outcomes like intubation and mortality, is clinically relevant.

Future research should aim to address these remaining uncertainties. Trials incorporating more sophisticated physiological monitoring—such as esophageal manometry to assess respiratory effort and transpulmonary pressures, electrical impedance tomography to evaluate regional ventilation and recruitment, or detailed analysis of breathing patterns—could provide deeper insights into the differential physiological effects of HFNC and NIPPV and help identify which patients are most likely to benefit from each modality. Furthermore, studies focusing on highly selected AHRF populations, defined by specific etiological or pathophysiological characteristics, are needed. For instance, a trial comparing HFNC and NIPPV specifically in patients with AHRF due to non-pneumonia ARDS, or in those with clearly defined high versus low recruitability, could yield more targeted evidence. The development and validation of early predictors of failure for both HFNC and NIPPV remain a priority, as timely recognition of non-responders and prompt escalation to intubation are crucial to avoid the adverse consequences of prolonged, ineffective non-invasive support, such as increased P-SILI, delayed initiation of potentially life-saving invasive ventilation, and worse outcomes. Moreover, the impact of different interface types for NIPPV (oronasal vs. full-face vs. helmet) in the context of AHRF is another area where more comparative data would be beneficial, as helmet NIPPV, for instance, has shown promise in some settings for improving tolerance and reducing air leaks, potentially altering the risk-benefit balance compared to traditional mask NIPPV.

5. Conclusion

In adult patients with Type 1 acute hypoxemic respiratory failure, this systematic review and meta-analysis of six randomized controlled trials found no statistically significant difference between high-flow nasal cannula oxygen therapy and non-invasive positive pressure ventilation concerning rates of endotracheal intubation or all-cause mortality. Furthermore, improvement in oxygenation at 24 hours and hospital length of stay were also comparable between the two interventions. These findings suggest that both HFNC and NIPPV are viable initial non-invasive respiratory support strategies for this patient population. The decision to use one modality over the other should be individualized based on factors such as patient tolerance, severity of illness, underlying etiology, institutional protocols, and clinician

experience. Regardless of the chosen method, vigilant patient monitoring and timely escalation to invasive mechanical ventilation are crucial for those who fail to respond to non-invasive support. Further research is needed to refine patient selection criteria and optimize the application of these valuable respiratory support tools.

6. References

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