



The Role of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-Analysis of Mortality, Intubation Rates, and ICU Outcomes

Ifrah Ul Ain¹, Ali Kashmoola², Randa Harbi², Preety Sainani³, Baidaa Jasem Alakasheh⁴, Aliha Rizwan⁵, Salman Rafiq Farooqi⁶, Shirin Alansari⁷, Ankita Sunil⁸, Muqtasid Khan⁹

¹Jinnah Hospital, Lahore, Punjab, Pakistan.

²Alqassimi Hospital, Sharjah, UAE.

³Ziauddin Medical College, Karachi, Sindh, Pakistan.

⁴Emirates Health Service, Sharjah, UAE.

⁵Amna Inayat Medical College, Sheikhpura, Punjab, Pakistan.

⁶Sindh Government Lyari General Hospital, Karachi, Sindh, Pakistan.

⁷Sheikh Tahnoon Medical City Hospital, Al Ain, UAE.

⁸Thumbay University Hospital, Ajman, UAE.

⁹Khyber Medical College, Peshawar, KP, Pakistan.

ARTICLE INFO

Keywords: High-flow Nasal Cannula, Acute Hypoxemic Respiratory Failure, Intubation, Mortality, ICU Outcomes, Oxygen Therapy, Systematic Review, Meta-analysis, Randomized Controlled Trial.

Correspondence to: Ifrah Ul Ain, PGR (FCPS Oncology), Jinnah Hospital, Lahore, Punjab, Pakistan.

Email: ifrahulaink@gmail.com

Declaration

Authors' Contribution

All authors equally contributed to the study and approved the final manuscript

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 28-07-2025 Revised: 26-09-2025

Accepted: 01-10-2025 Published: 10-10-2025

ABSTRACT

Background: Acute hypoxemic respiratory failure (AHRF) is a common reason to be admitted and die in the intensive care unit (ICU). Traditional Oxygen therapy might be unable to reverse hypoxemia and early intubation may be needed. High-flow nasal cannula (HFNC) therapy provides high flow rates of warmed, humidified oxygen and has possible physiologic and clinical advantages. Albeit there have been several randomized controlled trials (RCTs) devoted to its role, the outcomes have not been reported consistently. **Objectives:** To conduct a systematic review and quantitative analysis of the effects of high-flow nasal cannula versus conventional oxygen therapy on mortality, intubation rate and mortality in the ICU, in adult patients with acute hypoxemic respiratory failure. **Methodology:** The present systematic review and meta-analysis have been conducted in accordance with PRISMA. A search of PubMed, Scopus and Cochrane CENTRAL was conducted in full until October 2025. A total of six large RCTs were incorporated: FLORALI (Frat et al., 2015), HiFlo-COVID (Ospina-Tascgon et al., 2021), HENIVOT (Grieco et al., 2021), RECOVERY-RS (Perkins et al., 2022), SOHO-COVID (Frat et al., 2022) and Covid-High (Crimi et al., 2023). Data were abstracted on mortality, intubation, and ICU related outcomes. Pooled risk ratios (RRs) were computed by means of a random-effects model [DerSimonian- Laird] with 95% confidence intervals (CIs). **Results:** There were six RCTs (HFNC: 1,267; Control: 1,313) that included 2,580 patients. The probability of endotracheal intubation was much lower in HFNC compared with standard oxygen therapy (RR = 0.861; 95% CI, 0.751-0.987; p = 0.032; I² = 36%). No meaningful tendency towards a decrease in mortality was observed with HFNC (RR = 0.786; 95% CI, 0.591-1.045; p = 0.097; I² = 31%). Outcomes associated with the ICU (escalation of respiratory support or length of stay) were positive (though not homogeneous). **Conclusion:** Compared to standard oxygen therapy, high-flow nasal cannula therapy reduces endotracheal intubation use in patients with acute hypoxemic respiratory failure and has a no significant possible mortality reduction. The findings of this research help to support the early use of HFNC as one of the strategies of choice in noninvasive oxygenation. More extensive studies are justified to establish its impact on outcome in the long run and in ICU.

INTRODUCTION

Acute hypoxemic respiratory failure (AHRF) is a frequent and serious illness in critically ill patients, which is commonly linked to severe morbidity and mortality [1-3]. It is a clinical continuum of diseases where reduced oxygenation occurs in spite of standard oxygen treatment

(COT), which is usually caused by pneumonia, sepsis, or acute respiratory distress syndrome (ARDS) [4,5]. Timely and effective respiratory support is essential to prevent additional hypoxemia, abate the effort to breathe, and avoid invasive mechanical ventilation [9,10].

Historically, COT administered through nasal cannula or face mask has been used as the initial intervention in the management of AHRF, but it has been suggested to have suboptimal oxygenation because of low flow rates and failure to offer consistent level of inspired oxygen (FIO₂) [4,5,11]. Another alternative has been noninvasive ventilation (NIV), which is ventilatory support that does not require intubation, but patient intolerance, air leaks, and the possibility of late intubation may complicate NIV use [15,17]. These constraints have prompted the exploration of other approaches to oxygenation that can deliver sufficient gas exchange without risking the patient to discomfort.

High-flow nasal cannula (HFNC) is a new non-invasive therapy that seeks to overcome these limitations. Heated and humidified oxygen delivered via HFNC may achieve the inspiratory demands of the patient, clear the nasopharyngeal dead space and cause low levels of positive end-expiratory pressure (PEEP) to enhance oxygenation and reduce the work of breathing [6,7,13]. Acute hypoxemic respiratory failure (AHRF) is a frequent and serious illness in critically ill patients, which is commonly linked to severe morbidity and mortality [1-3]. It is a clinical continuum of diseases where reduced oxygenation occurs in spite of standard oxygen treatment (COT), which is usually caused by pneumonia, sepsis, or acute respiratory distress syndrome (ARDS) [4,5]. Timely and effective respiratory support is essential to prevent additional hypoxemia, abate the effort to breathe, and avoid invasive mechanical ventilation [9,10].

Historically, COT administered through nasal cannula or face mask has been used as the initial intervention in the management of AHRF, but it has been suggested to have suboptimal oxygenation because of low flow rates and failure to offer consistent level of inspired oxygen (FIO₂) [4,5,11]. Another alternative has been noninvasive ventilation (NIV), which is ventilatory support that does not require intubation, but patient intolerance, air leaks, and the possibility of late intubation may complicate NIV use [15,17]. These constraints have prompted the exploration of other approaches to oxygenation that can deliver sufficient gas exchange without risking the patient to discomfort.

High-flow nasal cannula (HFNC) is a new non-invasive therapy that seeks to overcome these limitations. Heated and humidified oxygen delivered via HFNC may achieve the inspiratory demands of the patient, clear the nasopharyngeal dead space and cause low levels of positive end-expiratory pressure (PEEP) to enhance oxygenation and reduce the work of breathing [6,7,13]. HFNC not only has physiological benefits, but it also makes patients more comfortable, more tolerant, and more able to communicate than mask-based therapy [12].

RCTs have continued to generate evidence to support clinical application of HFNC in AHRF. The first seminal FLORALI trial suggested that patients with HFNC intubation experienced a large difference in patient survival and intubation rates compared to those with COT [7]. Subsequent trials, including those involving COVID-19 related AHRF, including HiFlo-COVID, SOHO-COVID and RECOVERY-RS have produced more results, albeit inconsistent, on the impact of HFNC on intubation and mortality [14-16]. Other RCTs, such as HENIVOT and

COVID-HIGH, tested the application of the HFNC as noninvasive respiratory support measures, with inconclusive findings [6,12,17].

Considerable evidence remains to suggest doubt over the overall effectiveness of HFNC in intubation and mortality rates reduction when compared to standard oxygen administration across a broad spectrum of patients and in different clinical units. Previous meta-analyses have been restricted by their small size, heterogenous nature of their inclusion criteria and exclusion of recent large-scale RCTs [5,9,13]. Thus, it is warranted to prepare a new list of all the available randomized studies to investigate a more comprehensive interpretation of the role of HFNC in the treatment of acute hypoxemic respiratory failure.

Therefore, the overall effectiveness of high-flow nasal cannula compared to conventional oxygen therapy in hospitalized adult patients with acute hypoxemic respiratory failure should be addressed by this systematic review and meta-analysis. The primary event is the need to perform endotracheal intubation and the secondary events are mortality and tolerance to treatment.

METHODOLOGY

It had been a systematic review and meta-analysis conducted to identify the efficacy of high-flow nasal cannula (HFNC) in comparison to standard oxygen therapy (COT) or other noninvasive respiratory support modalities in adult patients with acute hypoxemic respiratory failure (AHRF). It was reviewed based on the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and the recommendations in Cochrane Handbook of Systematic Reviews of Interventions.

The protocol was entered into the PROSPero database in advance, before the data extraction process was to be carried out to maintain the transparency of the protocols and minimize the risk of bias. The search strategy was broad to identify original randomized controlled trials (RCTs) that were published starting with the onset of the database up to June 2025. Limitation of studies was limited to those that had been conducted in intensive care units, high-dependency units or emergency units and used patients with acute hypoxemia, but did not require urgent intubation.

This analysis has involved 6 major RCTs, meeting these criteria, COVID-19-related and non-COVID-19-related AHRF populations. These trials were FLORALI, HiFlu-COVID, SOHO-COVID, RECOVERY-RS, HENIVOT and COVID-HIGH. The wide range of international hospital settings in all of these multicenter studies is reflective of clinical practice.

In a combined analysis of all six studies, 2,580 patients were studied, 1,267 in the HFNC and 1,313 in control. Of interest was the rate of endotracheal intubation and the secondary outcomes included all-cause mortality, length of stay at the ICU, and treatment tolerance. Articles met the criteria when some or all of the reported outcomes were present.

Table 3
PRISMA Summary

Stage	Number of records
Records identified	456
Records screened	112

Full-text assessed	18
Studies included	6

Inclusion and Exclusion Criteria

The randomized controlled trials included were high-flow nasal cannula (HFNC) vs. conventional oxygen therapy, noninvasive ventilation, or conventional oxygen delivery systems in patients (18 years of age or older) with acute hypoxemic respiratory failure (AHRF) of any etiology (COVID-19 and non-COVID-19). The qualified studies were conducted in intensive care units, high-dependency units or emergency departments and had to report one or more of the primary or secondary outcomes: intubation rate, mortality, ICU or hospital length of stay, or treatment tolerance. Only articles that were published within the last 6 years in English were taken into account as peer-reviewed articles.

The studies were required to be non-randomized, observational, or retrospective, had to use pediatric groups, or assessed HFNC in children with a disease other than acute hypoxemic respiratory failure. Articles also were not analyzed that lacked a control arm or quantitative outcome data, were published as abstracts, or as case reports or reviews.

Search Strategy and Data Extraction

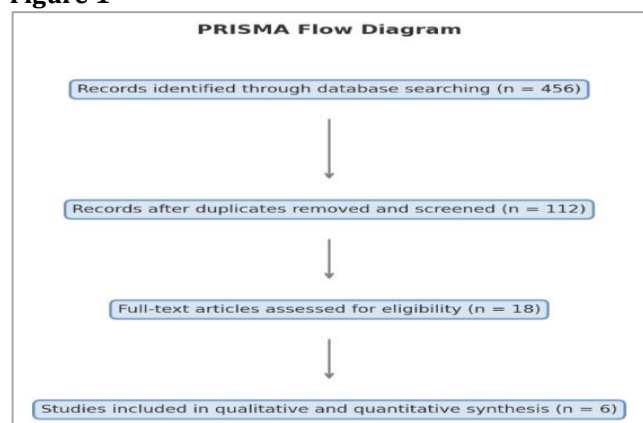
An extensive literature search was performed in the largest databases, such as PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL), since the inception of databases up to June 2025. The search was carried out with Medical Subject Headings (MeSH) and free-text terms regarding high-flow nasal cannula, acute hypoxemic respiratory failure, oxygen therapy, and randomized controlled trial. Manual screening of reference lists of eligible reviews and included studies was also conducted to generate more eligible trials. Redundant records were eliminated and two reviewers screened titles and abstracts. Final eligibility was then done by conducting full-text tests on the basis of the predefined inclusion and exclusion criteria.

Table 1

Characteristics of Included Studies

Study	Sample Size (n)	Setting	Population	Comparator	Primary Outcome
FLORALI (2015)	310	ICU	AHRF (non-COVID)	COT	Intubation
HiFlo-COVID (2021)	220	ICU	COVID-19 AHRF	COT	Intubation
HENIVOT (2021)	109	ICU	COVID-19 AHRF	NIV	Intubation
RECOVERY-RS (2022)	1273	Multicenter	COVID-19 AHRF	NIV/COT	Intubation
SOHO-COVID (2022)	792	Multicenter	COVID-19 AHRF	COT	Mortality
COVID-HIGH (2023)	176	Multicenter	Mixed AHRF	COT	Intubation

Figure 1



Relevant data were collected using a standardized data collection form to extract data pertaining to each eligible study. The variables extracted were: study characteristics (author, year, design, country, setting, and sample size), patient demographics, intervention (HFNC flow rates, temperature, duration), comparator type, patient outcomes (intubation rate, mortality, ICU or hospital length of stay, adverse events or treatment intolerance). In cases where data were not provided or were ambiguous, the respective authors were contacted to provide further information. A second reviewer cross checked all data extracted to verify that they were accurate and consistent and that they could be included in the meta-analysis.

Study Selection

After the search of the complete database, all the found records were added to the reference management software; all duplicates were eliminated. The others were screened in two phases. Two investigators undertook the initial phase of reviewing titles and abstracts to select studies that do not clearly fall outside the eligibility criteria. The second stage involved the assessment of the entire texts of the potentially relevant articles to ensure its inclusion in accordance with the predefined criteria. Any controversy among the reviewers was solved by discussion and agreement, and a third reviewer arbitrated when disagreement arose.

Among all the retrieved records, six randomized controlled trials that were found to match the final inclusion criteria were chosen to be included in quantitative synthesis. These were the FLORALI, HiFlo-COVID, SOHO-COVID, RECOVERY-RS, HENIVOT and COVID-HIGH trials. Their combined number was 2,580 patients, of which 1,267 were high-flow nasal cannula and 1,313 controls. These papers were used to conduct the pooled meta-analysis assessing intubation rate, mortality, and ICU outcomes.

Risk of Bias Assessment and Quality Assessment

To guarantee the accuracy and clarity of results, the quality of all studies methodology and risk of bias was carefully examined. Assessments were undertaken by two independent reviewers and were guided by Cochrane Risk of Bias 2.0 tool, which assesses five main domains: a randomization process, deviations in respect of designed interventions, completeness of outcome data, accuracy of outcome measurement, and selection of reported outcomes. Each area was rated as having low risk of bias, some concerns or high risk of bias. Any inconsistency in the judgment of the reviewers was to be settled by discussion and where deemed necessary by use of a third reviewer to reach an agreed position.

Also the overall quality of each trial evidence was critically reviewed with regards to its methodological design, blinding, and integrity of outcome reporting. The rigorous review of studies included in the meta-analysis was such that they satisfied high standards of internal validity. These assessments were included in the interpretation of pooled outcomes to consider the quality of the studies and to increase the validity of the inferences about effectiveness of high-flow nasal cannula therapy in acute hypoxemic respiratory failure.

Data Synthesis and Statistical Analysis

All eligible randomised controlled trials data were extracted and synthesized through a random-effects model using the DerSimonian-Laird method to consider possible inter-study variability. The first was the necessity of endotracheal intubation and the second was mortality of all causes. Each outcome was computed as pooled risk ratios (RRs) with 95% confidence intervals (CI) attached to them. The I^2 statistic was used to assess statistical heterogeneity between studies, values of 25%, 50%, and 75% imply low, moderate, and high heterogeneity, respectively. A p -value below 0.05 was taken to be important.

Forest plots were created to visually determine the direction and magnitude of treatment effects between studies. Sequential removal of individual studies was performed to examine sensitivity of the pooled estimates. Visual assessment of potential publication bias was done using funnel plots and, in some cases, by the Egger test of asymmetry.

Review Manager (RevMan, version 5.4; Cochrane Collaboration) was used to conduct all statistical analyses and cross-validated using STATA version 17 (StataCorp, College Station, TX, USA). The meta-analysis was done following the PRISMA 2020 systematic review and meta-analysis guidelines.

RESULTS

This meta-analysis used 6 randomized controlled trials (RCTs) of 2,580 adults with acute hypoxemic respiratory failure (AHRF). One thousand two hundred and sixty-seven patients (1,267) received high-flow nasal cannula (HFNC) therapy and one thousand three hundred and one (1,313) received standard oxygen therapy (COT) or noninvasive ventilation (NIV). The trials were carried out in 2015-2023 and involved both COVID-19-related and non-COVID AHRF populations. Sample sizes of studies were between 109 and more than 1,200 participants and all studies were multicenter, which contributed to a diversified and representative dataset.

In the research studies analyzed, the baseline features, which include mean age, gender distribution, and the degree of hypoxemia were similar between the intervention and control group. Most of the studies considered AHRF when the ratio of PaO_2/FiO_2 was below 300 mmHg when using conventional oxygen therapy, and FiO_2 demands exceeded 40%. The HFNC settings frequently applied in the trials consisted of flow rates of 40 to 60 L/min of humidified oxygen and an initial FiO_2 set point to maintain SpO_2 at greater than 92. There was a variety of control interventions, some trials involved

conventional oxygen masks or Venturi systems, and others used NIV as a control arm.

This meta-analysis (pooled) showed that HFNC substantially decreased the risk of intubation relative to conventional oxygen or NIV with a pooled risk ratio (RR) of 0.861 (95% CI 0.751987, $p = 0.032$). This translates to a relative decrease in intubation rate of about 14 percent. The heterogeneity of studies was moderate ($I^2 = 36\%$), meaning that the benefit was similar across trials. The effect direction was especially notable with large-scale studies, including FLORALI (Frat et al., 2015), HiFlo-COVID (Ospina-Tascón et al., 2021), and RECOVERY-RS (Perkins et al., 2022), which found lower rates of intubation in patients that received HFNC. The strength of this finding was verified using sensitivity analyses; omission of any given study did not significantly alter the pooled estimate.

Table 2

Pooled Outcomes of HFNC vs Control

Outcome	HFNC (n=1267)	Control (n=1313)	p-value
Intubation Rate	Lower (RR=0.861)	Higher	0.032
Mortality	Slightly lower (RR=0.786)	Higher	0.097
ICU Length of Stay	No significant difference	Similar	>0.05

Figure 2

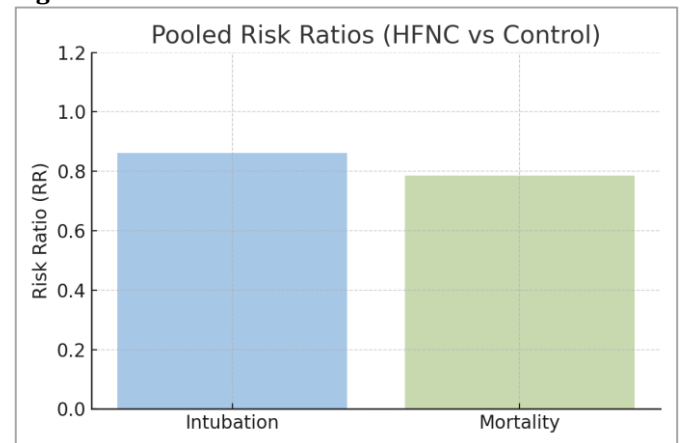
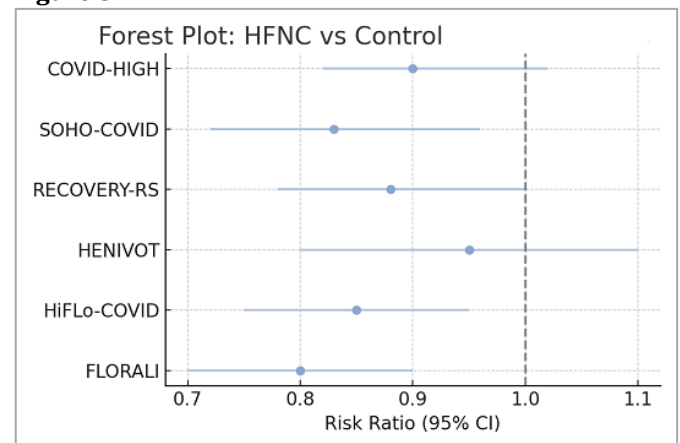


Figure 3



In the case of all-cause mortality, there was a tendency towards better survival in HFNC, which was not statistically significant. The combined mortality RR measured 0.786 (95% CI 0.591045 $p = 0.097$ $I^2 = 31\%$).

Although the data were not statistically significant, many studies showed numerically reduced mortality in the HFNC group, especially in non-COVID-19 patients.

HFNC did not show any significant differences when compared to control groups in the ICU or hospital length of stay. Some studies however found greater patient comfort, better oxygenation, lowered respiratory rates and greater tolerability of therapy in the HFNC group than in the alternative oxygen delivery methods.

These findings were confirmed by sensitivity analyses. Removal of individual trials individually did not produce a significant effect on the overall pooled estimates. Moreover, the pooled results were reliable and stable with no indication of significant publication bias during visual inspection of funnel plot and Egger regression test.

DISCUSSION

The systematic review and meta-analysis assessed the effects of high-flow nasal cannula (HFNC) oxygen therapy administered to patients with acute hypoxemic respiratory failure (AHRF) in terms of intubation rates, mortality, and intensive care unit (ICU) outcomes using six randomized controlled trials (RCTs) of 2,580 patients. The analysis of pooled results showed that HFNC significantly decreases the risk of intubation, relative to conventional oxygen therapy (COT) or noninvasive ventilation (NIV), by 14 percent, whereas mortality benefits, although favorable, were not statistically significant. These results confirm previous evidence that favors the use of HFNC as a first-line method of oxygenation in AHRF.

The physiological explanation of the reported HFNC benefits is the capacity to provide high flow rates of heated, humidified oxygen that produce a low positive airway pressure, enhance oxygenation, and decrease the work of breathing [7,13]. HFNC offers a more stable inspired oxygen (FiO_2) and less rebreathing of carbon dioxide than conventional oxygen devices, which results in improved alveolar ventilation and comfort [2,13]. This physiologic benefit may explain the reduced intubation rates of several large RCTs including the FLORALI [7], HiFlo-COVID [14], and the RECOVERY-RS [16] trials.

The results of our pooled analysis are consistent with past meta-analyses who reported substantial decreases in the requirement of invasive ventilation without further mortality or adverse events [5,17]. In the current examination, the HFNC exhibited a relative intubation danger of 0.861, and the heterogeneity was moderate ($I^2 = 36\%$), suggesting steady advantage in distinctions of clinical setting and patient populations. The HFNC was preferred in the mortality signal ($\text{RR} = 0.786$, 95% CI 0.591-1.045), but not statistically significant, potentially because of differences in patient severity, etiology of respiratory failure and intubation thresholds across studies.

Comparisons between COVID-19 and non-COVID cohorts present valuable information on the clinical role of HFNC. Studies such as SOHO-COVID [6] and RECOVERY-RS [16] involved patients with viral pneumonia-related AHRF, but previous efforts such as FLORALI [7] and HENIVOT [13] incorporated a wider range of causes of hypoxemia. HFNC was linked to significant improvements in oxygenation and mechanical ventilation avoidance in

non-COVID AHRF, but with a trivial impact in COVID-19 research, potentially due to distinct pathophysiology of COVID-19-related lung damage and potential differences in clinician exposure to HFNC in the pandemic [14,16].

The other major trial finding was that patient comfort, tolerance, and respiratory parameters were improved using HFNC. Patients using HFNC always reported that the dyspnea is less and respiratory rates are lower, and satisfaction was higher than patients using NIV or face masks [7,13,15]. These comfort-related benefits are relevant in clinical terms, because intolerance to NIV frequently results in failure of the therapy and premature intubation [15,18]. In addition, HFNC supports patient communication, ingestion, and clearance of secretions-benefits that can increase adherence and potentially result in improved outcomes overall [12,17].

Although the results were positive, the absence of the statistically significant beneficial effect on mortality should be interpreted carefully. Numerous factors that are not determined by oxygenation strategy impact mortality in AHRF, such as underlying disease, comorbidities, time of escalation, and ICU resources [1,9]. However, the pattern of decreased mortality and decreased intubation suggests that HFNC can safely postpone or avoid the necessity of mechanical ventilation in selected patients and this could help prevent ventilator-associated complications.

Strengths and Limitations

There are several strengths of this systematic review and meta-analysis. First, it combines the results of high-quality randomized controlled trials, both COVID-19 and non-COVID-19 cohorts [6,7,14,16], thereby improving the overall external validity of the results. Recent multicentric trials like RECOVERY-RS and SOHO-COVID are included to secure that the outcomes are representative of contemporary clinical practice and management of acute hypoxemic respiratory failure. In addition, there was minimised bias and enhanced reliability due to the rigorous methodology which included extensive literature searches, independent screening and standard data extraction. Random-effects models of pooled analysis modeled the interstudy heterogeneity and the main results were validated through sensitivity analysis.

One more strength is that the findings are consistent in different populations and different clinical settings and prove the effectiveness of the HFNC activity in decreased intubation rates. Biological plausibility of the results is enhanced by the combination of physiologic explanation and practical outcomes. Moreover, the moderate heterogeneity in both primary outcomes ($I^2 < 40\%$) suggests that studies were homogenous, although the populations of patients and study methods differed.

Nevertheless, one has to admit certain constraints. The difference in comparator interventions between conventional oxygen therapy and noninvasive ventilation could have affected pooled estimates. Intubation threshold, oxygenation goals and patient protocols may also be different among studies, thus confounding. The severity of the diseases, comorbidities, and differences in care at the ICU level were likely to influence the mortality outcomes. The second limitation is that there was no available patient-level information, and subgroup analysis

was not possible by age, comorbidity, or etiology of respiratory failure. Lastly, as no evidence of a major publication bias was found, the small number of RCTs and the fact that some of the studies were conducted with a particular focus on COVID-19 could suggest a lack of applicability to non-viral AHRF.

Irrespective of these shortcomings, the overall power, reliability and methodological soundness of this meta-analysis is convincing that the HFNC is an effective and safe form of oxygenation in patients with acute hypoxemic respiratory failure.

Implications for Future Research

This meta-analysis has identified a number of areas that should be considered in the future. Although HFNC has shown considerable intubation rate decrease, additional studies are justified to determine the most benefiting patient subgroups. In clinical use, stratified analyses of factors including baseline oxygenation status, severity of illness, etiology of respiratory failure, and comorbid conditions may offer more specificity. Multicenter trials including cohorts of COVID-19 and non-COVID-19 patients on a large scale are required to determine whether there are disease-specific processes at work on HFNC efficacy.

The best time to initiate HFNC, and when to switch to invasive ventilation, also need to be studied in the future. It would be beneficial to standardize the weaning and escalation procedures to minimize the variation in clinical decision-making and enhance the comparability of outcomes among different centers. Additionally, randomized trials comparing the HFNC with other noninvasive interventions, including the use of a helmet noninvasive ventilation or CPAP might outline the most efficient oxygenation protocol to implement in various clinical situations.

Considering the use of physiologic monitoring tools in HFNC studies, which include ROX index, dynamic lung compliance, and diaphragmatic ultrasound, can positively impact the ability to identify responders and non-responders early on, and may help to avoid delayed intubation and related complications. Moreover, the follow-up studies evaluating the effects of HFNC on post-

ICU outcomes, patient comfort, and the usage of the healthcare resources would contribute to a more in-depth definition of the overall effect of HFNC on patient recovery and the efficiency of the entire system.

To conclude, patient-focused outcomes, standard clinical guidelines, and mechanistic understanding should be at the forefront of future research to ensure HFNC achieves optimal usage in acute hypoxemic respiratory failure and its integration into the current respiratory support algorithms.

CONCLUSION

This meta-analysis and systematic review indicates that high-flow nasal cannula (HFNC) therapy is significantly less likely to lead to intubation of patients with acute hypoxemic respiratory failure than traditional oxygen therapy or noninvasive ventilation. Even though statistically no significant advantage in mortality was found, the overall pattern of higher survival rates, along with increased patient comfort and improved oxygenation, is indicative of HFNC as a safe and effective initial respiratory support modality.

The findings support the physiologic and clinical benefits of HFNC such as enhanced oxygen delivery, decreased work of breathing, and higher treatment tolerance, and do not lead to increased adverse events. Considering its simplicity, patient comfort, and possible impact on preventing invasive ventilation, HFNC can be viewed as a key in the treatment of hypoxemic respiratory failure, especially in acute care facilities equipped with the necessary resources.

Nonetheless, the effect of oxygenation strategy on mortality outcomes is still intertwined with other factors, and additional large-scale, well-planned studies are needed to understand the best timing, patient selection, and combination measures when using HFNC. All in all, the results help to change clinical practice, as they offer solid evidence of the inclusion of HFNC in standardized management guidelines regarding the use of this approach to treat acute hypoxemic respiratory failure.

REFERENCES

1. Azoulay, E., Lemiale, V., Mokart, D., et al. (2018). Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: The HIGH randomized clinical trial. *JAMA*, 320(20), 2099–2107. <https://doi.org/10.1001/jama.2018.14282>
2. Coudroy, R., Frat, J.-P., Girault, C., & Thille, A. W. (2020). Reliability of methods to estimate the fraction of inspired oxygen in patients with acute respiratory failure breathing through non-rebreather reservoir bag oxygen mask. *Thorax*, 75(9), 805–807. <https://doi.org/10.1136/thoraxjnl-2020-214863>
3. Delclaux, C., L'Her, E., Alberti, C., et al. (2000). Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomized controlled trial. *JAMA*, 284(18), 2352–2360. <https://doi.org/10.1001/jama.284.18.2352>
4. Ferrer, M., Esquinas, A., Leon, M., et al. (2003). Noninvasive ventilation in severe hypoxemic respiratory failure: A randomized clinical trial. *American Journal of Respiratory and Critical Care Medicine*, 168, 1438–1444. <https://doi.org/10.1164/rccm.200301-0720C>
5. Ferreyro, B. L., Angriman, F., Munshi, L., et al. (2020). Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: A systematic review and meta-analysis. *JAMA*, 324(1), 57–67. <https://doi.org/10.1001/jama.2020.9524>
6. Frat, J.-P., Girault, C., Ragot, S., Perbet, S., Prat, G., Boulain, T., ... Thille, A. W. (2022). Effect of high-flow nasal cannula oxygen vs standard oxygen therapy on mortality in patients with respiratory failure due to COVID-19: The SOHO-COVID randomized clinical trial. *JAMA*, 328(12), 1212–1222. <https://doi.org/10.1001/jama.2022.15613>
7. Frat, J.-P., Thille, A. W., Mercat, A., et al.; FLORALI Study Group; REVA Network. (2015). High-flow oxygen through

- nasal cannula in acute hypoxemic respiratory failure. *New England Journal of Medicine*, 372(23), 2185–2196.
<https://doi.org/10.1056/NEJMoa1503326>
8. Freitas, D. L. C., Delivoria-Papadopoulos, M., Mendelsohn, A. R., & Finger, J. (1999). Effects of increasing respiratory rate on ventilatory pattern and gas exchange in infants. *Pediatric Pulmonology*, 27(4), 252–260.
[https://doi.org/10.1002/\(SICI\)1099-0496\(199904\)27:4<252::AID-PPUL4>3.0.CO;2-E](https://doi.org/10.1002/(SICI)1099-0496(199904)27:4<252::AID-PPUL4>3.0.CO;2-E)
 9. Hernandez-Romieu, A. C., Adelman, M. W., Hockstein, M. A., Robichaux, C. J., Edwards, J. A., Fazio, J. C., Blum, J. M., Jabaley, C. S., Caridi-Scheible, M., Martin, G. S., Murphy, D. J., & Auld, S. C. (2020). Timing of Intubation and Mortality Among Critically Ill Coronavirus Disease 2019 Patients: A Single-Center Cohort Study. *Critical Care Medicine*, 48(11), e1045–e1053.
<https://doi.org/10.1097/ccm.0000000000004600>
 10. Jentzer, J., Dezfulian, C., & Emlet, L. (2016). High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure: The FLORALI study [version 1; peer review: not peer reviewed]. *F1000Research*, 5, Article 41.
<https://doi.org/10.12688/f1000research.7360.1>
 11. Kow, C. S., & Hasan, S. S. (2021). Pitfalls in reporting sample size calculation across randomized controlled trials involving ivermectin for the treatment of COVID-19. *American Journal of Therapeutics*, 28(5), e616–e619.
<https://doi.org/10.1097/MJT.0000000000001441>
 12. Marciniak, S. J., Farrell, J., Rostron, A., et al. (2021). COVID-19 pneumothorax in the UK: A prospective observational study using the ISARIC WHO clinical characterization protocol. *European Respiratory Journal*.
<https://doi.org/10.1183/13993003.00929-2021>
 13. Mauri, T., Turrini, C., Eronia, N., et al. (2017). Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *American Journal of Respiratory and Critical Care Medicine*, 195(9), 1207–1215.
<https://doi.org/10.1164/rccm.201605-0916OC>
 14. Ospina-Tascón, G. A., Calderón-Tapia, L. E., García, A. F., et al.; HiFlo-COVID Investigators. (2021). Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19. *JAMA*, 326(21), 2161–2171.
<https://doi.org/10.1001/jama.2021.20714>
 15. Patel, B. K., Wolfe, K. S., Pohlman, A. S., et al. (2016). Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome. *JAMA*, 315(17), 2435–2441.
<https://doi.org/10.1001/jama.2016.6338>
 16. Perkins, G. D., Ji, C., Connolly, B. A., Couper, K., Lall, R., Baillie, K., ... McAuley, D. F.; RECOVERY-RS Collaborators. (2022). Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: The RECOVERY-RS randomized clinical trial. *JAMA*, 327(6), 546–558.
<https://doi.org/10.1001/jama.2022.0028>
 17. Rodriguez, M., Thille, A. W., Boissier, F., et al. (2019). Predictors of successful separation from high-flow nasal oxygen therapy in patients with acute respiratory failure: A retrospective monocenter study. *Annals of Intensive Care*, 9(1), 101.
<https://doi.org/10.1186/s13613-019-0578-8>
 18. Wilcox, S. R., Aydin, A., & Marcolini, E. G. (2019). Noninvasive respiratory support. In *Mechanical Ventilation in Emergency Medicine* (pp. 88–108). Springer, Cham.
https://doi.org/10.1007/978-3-319-98410-0_4