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Original Research Article

High-Flow Nasal Cannula vs. Non-Invasive Ventilation for Post-Extubation Respiratory Failure: A Meta-Analysis

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Abstract

Background: High-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) are widely used after planned extubation, but their comparative effectiveness is uncertain because treatment effects may depend on baseline risk, hypercapnia, obesity, interface tolerance, humidification, and treatment intensity.

Methods: A focused aggregate-data reconstruction identified direct randomized comparisons in adults receiving prophylactic HFNC or NIV immediately after planned extubation. The primary outcome was reintubation within the trial-defined early window (48 hours to 7 days). Secondary outcomes were post-extubation respiratory failure, all-cause mortality at the longest reported follow-up, and intensive care unit (ICU) length of stay. Risk ratios (RRs) and mean differences (MDs) were synthesized with a Paule–Mandel random-effects model and modified Hartung–Knapp confidence intervals. Heterogeneity was summarized with I^2 and τ^2. Leave-one-out, fixed-effect, and exploratory small-study-effect analyses were performed.

Results: Seven randomized trials involving 1,572 adults contributed to the reintubation analysis. Reintubation occurred in 172/779 (22.1%) HFNC recipients and 166/793 (20.9%) NIV recipients. The pooled estimate showed no average difference but substantial inconsistency (RR 1.00, 95% CI 0.49–2.02; I^2=73.7%). HFNC was associated with less post-extubation respiratory failure in four trials (RR 0.69, 95% CI 0.52–0.91; I^2=0.0%). Mortality was not significantly different (RR 0.76, 95% CI 0.44–1.32; I^2=54.1%). Estimated ICU stay was 0.81 days shorter with HFNC, but the confidence interval included no effect (MD -0.81 days, 95% CI -1.78 to 0.16; I^2=0.0%). Leave-one-out analyses did not produce a stable statistically significant reintubation effect. Funnel-plot and Egger analyses were underpowered.

Conclusions: The average reintubation risk did not differ clearly between HFNC and NIV, but marked heterogeneity argues against treating them as interchangeable. HFNC may reduce post-extubation respiratory failure and improve tolerance, whereas actively humidified NIV may be preferable in selected very-high-risk, obese, or hypercapnic patients. Modality selection should be phenotype- and protocol-specific, with close monitoring and predefined escalation criteria.

Keywords: airway extubation; high-flow nasal cannula; non-invasive ventilation; post-extubation respiratory failure; reintubation; intensive care.

Introduction

Extubation is a high-risk transition in critical care. Even after a patient passes a spontaneous breathing trial, recurrent respiratory failure may occur because the spontaneous breathing trial does not fully reproduce the combined load imposed by airway secretions, upper-airway resistance, cardiac dysfunction, diaphragmatic weakness, gas-exchange abnormalities, and loss of positive end-expiratory pressure. Reintubation is consequently associated with increased infectious complications, longer intensive care exposure, and higher mortality [1–4].

Prophylactic non-invasive respiratory support is used to attenuate this vulnerable period. NIV can unload respiratory muscles, augment tidal ventilation, recruit lung volume, and improve hypercapnia or cardiogenic pulmonary edema.

Its effectiveness, however, depends on an adequate interface, sufficient pressure support, humidification, patient cooperation, and time on therapy. Mask discomfort, skin injury, aerophagia, impaired communication, secretion management difficulties, and interruptions in treatment may reduce its real-world effectiveness [5–8].

HFNC provides heated and humidified gas at high flow, reduces nasopharyngeal dead space, supplies a modest and variable distending pressure, stabilizes inspired oxygen concentration, and is usually better tolerated than a tight-fitting NIV interface.

These properties make HFNC attractive after extubation, particularly when prolonged continuous support is desirable or NIV is poorly tolerated. Nevertheless, HFNC provides less ventilatory assistance than NIV and may be insufficient for patients with severe hypercapnia, major inspiratory effort, obesity-related load, or a strong positive-pressure indication [9–12].

Direct randomized trials have produced discordant results. A large 2016 trial found HFNC non-inferior to NIV in a heterogeneous high-risk population, whereas later trials in very-high-risk and obese populations suggested a possible advantage for actively humidified NIV. Conversely, some single-center trials in COPD or mixed high-risk cohorts reported lower reintubation with HFNC [13–19].

Previous meta-analyses generally found no overall difference in reintubation or mortality, but their conclusions were limited by heterogeneous populations, endpoint windows, device protocols, and study quality [20–22].

The present publication-style model synthesizes directly extractable aggregate data to illustrate how a rigorous manuscript could report the comparative evidence. The objectives were to estimate pooled effects for reintubation and key secondary outcomes, quantify heterogeneity, explore the influence of individual trials and protocol differences, and provide a balanced clinical interpretation.

Methods

Design and Reporting Framework: The manuscript was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework [23]. Because this document is a focused evidence reconstruction rather than a prospectively conducted review, it does not claim complete database coverage or independent duplicate screening.

The analytic dataset was reconstructed from peer-reviewed trial reports, PubMed-indexed abstracts, open full texts, and recent systematic reviews available through 31 July 2026. A de novo submission should prospectively register

the protocol, preserve complete search logs, and use two independent reviewers at every eligibility, extraction, and risk-of-bias stage.

Eligibility Criteria: Studies were eligible for the quantitative reconstruction when they: (1) enrolled adults who underwent planned extubation after invasive mechanical ventilation; (2) compared HFNC with NIV initiated immediately or shortly after extubation as prophylactic support; (3) used randomized or randomized-comparative allocation; and (4) reported extractable events for reintubation or another prespecified outcome. Pediatric studies, rescue treatment initiated only after established post-extubation failure, combination NIV-plus-HFNC strategies, conventional oxygen comparators, observational studies, and retracted reports were excluded from the primary pooled dataset.

Population, intervention, comparator, and outcomes

Table 1: Eligibility framework and outcome definitions

Domain	Definition
Population	Adults receiving prophylactic non-invasive respiratory support after planned extubation.
Intervention	Heated, humidified HFNC, with flow and FiO_2 titrated to trial targets.
Comparator	NIV delivered through a mask or equivalent interface; humidification and duration varied.
Primary outcome	All-cause reintubation in the earliest trial-defined window from 48 hours through 7 days.
Secondary outcomes	Post-extubation respiratory failure; mortality at the longest reported follow-up; ICU length of stay; treatment intolerance and adverse effects narratively.
Effect direction	For adverse binary outcomes, RR <1 favors HFNC and RR >1 favors NIV. For ICU stay, MD <0 favors HFNC.

Information sources and search approach: A focused search used combinations of "high-flow nasal cannula," "high-flow nasal oxygen," "noninvasive ventilation," "NIV," "extubation," "post-extubation," "reintubation," and "randomized." PubMed-indexed records and full-text reports were cross-checked against recent systematic reviews and reference lists [20–22]. The 2026 Patil trial was added because it was published before the evidence cutoff and reported extractable event counts [19].

Study Selection and Data Extraction: For each included trial, the following variables were reconstructed: country and setting, sample size, clinical phenotype, risk criteria, HFNC and NIV protocols, humidification, treatment duration, outcome definition, event counts, and follow-up window. When multiple reintubation windows were available, the trial's primary early endpoint was used. For mortality, the longest reported follow-up with extractable counts was selected. Median ICU length of stay and interquartile ranges were converted to approximate means and standard deviations using established quantile-based methods [24,25]. These approximations were confined to a sensitivity-style secondary analysis.

Risk of Bias and Certainty of Evidence: A provisional study-level appraisal was organized around the Cochrane Risk of Bias 2 domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting [26]. Because respiratory-support interfaces preclude participant and clinician blinding, the assessment focused on allocation concealment, objective reintubation

criteria, crossover policy, completeness, PR specification, and consistency of reported statistics. The certainty of evidence was interpreted using GRADE principles, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias [27]. This provisional appraisal must be independently duplicated before journal submission.

Statistical Analysis: For dichotomous outcomes, study-specific log risk ratios and sampling variances were calculated from event counts. A 0.5 continuity correction was applied to all four cells of a study containing a zero event in one arm. Continuous outcomes were expressed as mean differences. The primary synthesis used a Paule–Mandel random-effects model. Confidence intervals were calculated using a modified Hartung–Knapp approach in which the variance inflation factor was not permitted to fall below 1. Statistical heterogeneity was assessed with Cochran's Q, τ^2, and I^2; I^2 values of approximately 25%, 50%, and 75% were interpreted as low, moderate, and high inconsistency [28–30].

Prespecified robustness analyses included a common-effect inverse-variance model, leave-one-out analysis, exclusion of the zero-cell prolonged-ventilation study, and exclusion of the two strongly HFNC-favoring single-center trials. Small-study effects were explored with a funnel plot and Egger regression only for the primary outcome.

Because fewer than 10 studies were available, publication-bias tests were considered underpowered and non-decisive [31]. Statistical calculations were reproduced in Python using NumPy, SciPy, pandas, statsmodels, and Matplotlib.

Results

Study Selection and Evidence Base: Seven randomized direct comparisons with extractable reintubation data were included in the primary reconstruction, comprising 1,572 adults (779 assigned to HFNC and 793 to NIV). The studies were conducted in Spain, Thailand, Egypt, Taiwan, and India and enrolled heterogeneous populations: general high-risk ICU patients, very-high-risk patients, patients with sepsis, high-risk COPD, prolonged ventilation, and obesity. Treatment duration ranged from 24 to 48 hours, and early reintubation endpoints ranged from 48 hours to 7 days. Additional studies using treatment-failure composites, non-randomized designs, combination strategies, or non-extractable outcome data were retained only for contextual discussion.

Study characteristics

2: Characteristics of trials included in the quantitative reconstruction

Study	Setting	N	Population	HFNC	NIV	Main endpoint
Hernández et al. [13]	Spain; 3 ICUs	604	Mixed high-risk	HFNC 24 h	NIV 24 h; humidification not central	Reintubation and respiratory failure, 72 h
Tongyoo et al. [14]	Thailand; medical ICU	222	Sepsis	HFNC; median 24 h	NIV; median 24 h	Reintubation, 72 h; mortality/LOS
Hernández et al. [15]	Spain; 2 ICUs	182	≥4 risk factors	HFNC 48 h	Actively humidified NIV 48 h	Reintubation, 7 d
Magdy & Metwally [16]	Egypt; single center	230	High-risk COPD	HFNC 48 h	NIV 48 h	Reintubation, 72 h; respiratory failure; 60-d mortality
Tseng et	Taiwan;	40	Prolonged	HFNC	NIPPV	Reintubation, 7 d;

al. [17]	single center		ventilation			90-d mortality
Hernández et al. [18]	Spain; 2 ICUs	144	Obesity; intermediate risk	HFNC 48 h	Actively humidified NIV 48 h	Reintubation, 7 d
Patil et al. [19]	India; single center	150	Mixed high-risk	HFNC 48 h	NIV with passive humidification 48 h	Reintubation, 48 h; respiratory failure, 7 d

Risk of Bias

Table 3: Provisional risk-of-bias assessment. This model assessment requires independent duplicate verification before submission

Study	Overall judgement	Principal rationale
Hernández 2016	Some concerns	Open-label interface; objective criteria but protocol and rescue decisions may influence reintubation.
Tongyoo 2021	Some concerns	Open-label, crossover between devices permitted before reintubation; otherwise balanced follow-up.
Hernández 2022	Low	Concealed randomized allocation, prespecified primary endpoint, active humidification, complete follow-up.
Magdy 2023	High	Single center, unusually large effect, open-label outcome decisions, and internal statistical/reporting concerns.
Tseng 2023	Some concerns	Very small sample, one zero-event arm, limited precision, and phenotype-specific population.
Hernández 2025	Low	Randomized multicenter protocol with complete follow-up; underpowered for superiority.
Patil 2026	Some concerns	Single center, open-label, passive NIV humidification, and potential performance/protocol effects.

Summary of pooled outcomes

Table 4: Random-effects summary of primary and secondary outcomes. RR <1 and MD <0 favor HFNC

Outcome	HFNC	NIV	Pooled effect (95% CI)	I^2	Interpretation
Reintubation, 48 h–7 d	172/779	166/793	RR 1.00 (0.49–2.02)	73.7%	No clear average difference; very imprecise because of high inconsistency.
Post-extubation respiratory failure	156/597	231/609	RR 0.69 (0.52–0.91)	0.0%	Fewer events with HFNC in the extractable subset.
Mortality, longest follow-up	106/617	127/629	RR 0.76 (0.44–1.32)	54.1%	No statistically reliable mortality difference.
ICU length of stay	—	—	MD -0.81 d (-1.78 to 0.16)	0.0%	Possible small reduction with HFNC; CI includes no effect; converted data.

Primary outcome: reintubation: Reintubation occurred in 172 of 779 HFNC recipients (22.1%) and 166 of 793 NIV recipients (20.9%). The pooled random-effects estimate was RR 1.00 (95% CI 0.49–2.02), indicating no clear average difference. Heterogeneity was substantial (I^2=73.7%, τ^2=0.440, Q=22.83, p=0.001). Trial effects ranged from strong benefit with HFNC in two single-center studies to benefit with actively humidified NIV in very-high-risk and obese cohorts. This dispersion, rather than the pooled point estimate alone, is the principal finding.

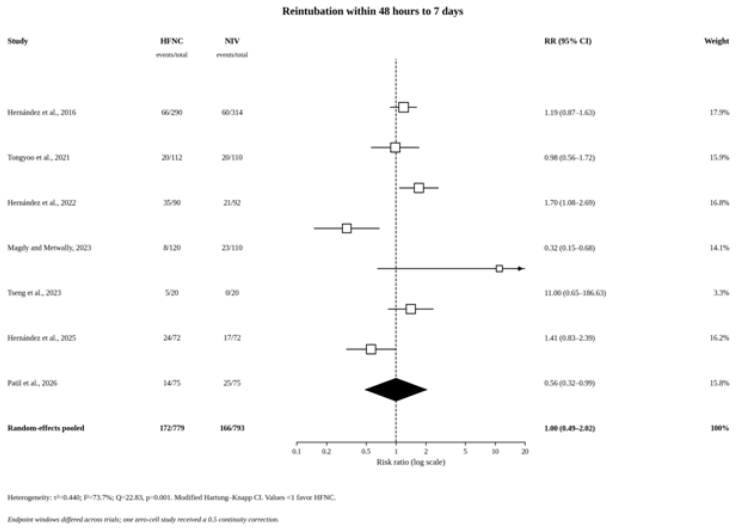

Figure 1: Forest plot of reintubation after planned extubation. Each square shows the study-specific risk ratio, the horizontal line its 95% confidence interval, square size the random-effects weight, and the diamond the pooled effect

Secondary outcome: post-extubation respiratory failure

Four trials with compatible event counts included 1206 participants. Post-extubation respiratory failure occurred in 156/597 HFNC recipients and 231/609 NIV recipients. HFNC was associated with a lower pooled risk (RR 0.69, 95% CI 0.52–0.91; I^2=0.0%).

The low statistical heterogeneity should not be interpreted as complete clinical homogeneity because outcome definitions, rescue rules, and observation windows differed.

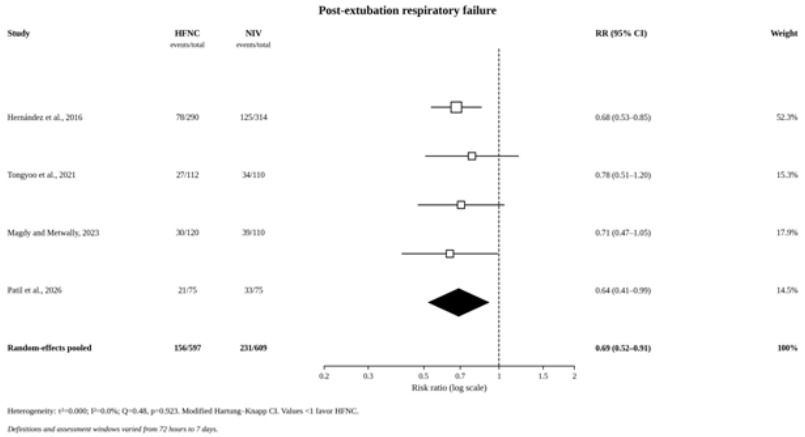

Figure 2: Forest plot of post-extubation respiratory failure

Secondary outcome: mortality: Five trials reported extractable all-cause mortality at follow-up ranging from hospital discharge to 90 days. Mortality occurred in 106/617 HFNC recipients and 127/629 NIV recipients. The pooled RR was 0.76 (95% CI 0.44–1.32; I^2=54.1%). The confidence interval included clinically important benefit and harm, and follow-up windows were not uniform; therefore, the mortality result is inconclusive.

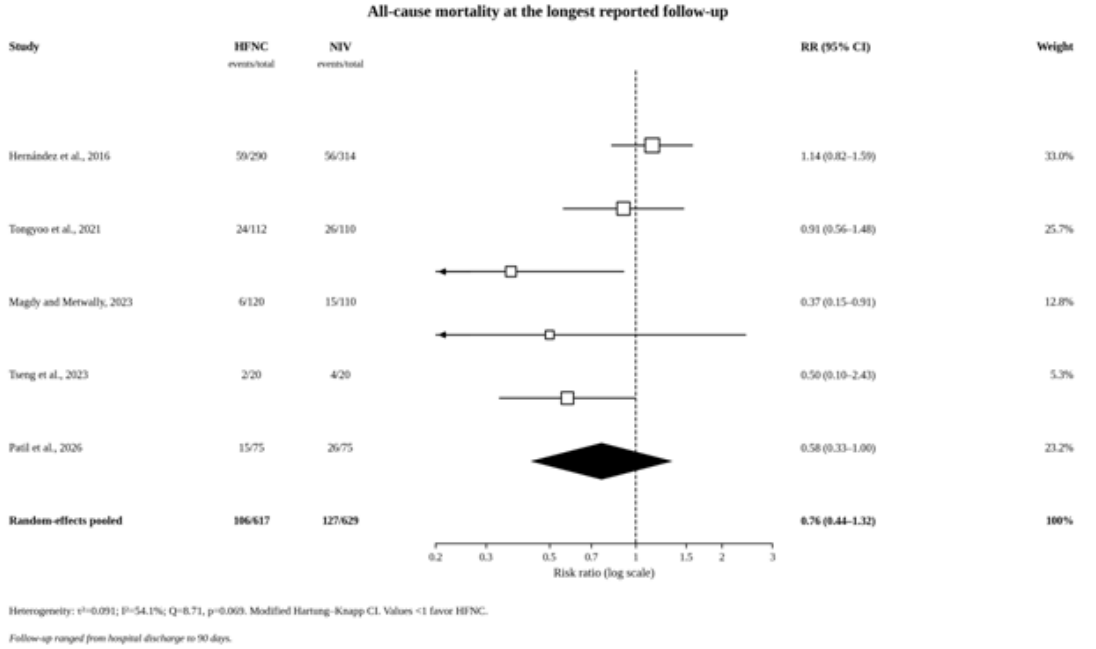

Figure 3: Forest plot of all-cause mortality at the longest reported follow-up

Secondary outcome: ICU length of stay

Four trials reported ICU length of stay as medians and interquartile ranges. After approximate conversion, HFNC was associated with a mean ICU stay 0.81 days shorter than NIV (MD -0.81 days, 95% CI -1.78 to 0.16; I^2=0.0%). The confidence interval crossed no effect, and the conversion of skewed length-of-stay data limits certainty.

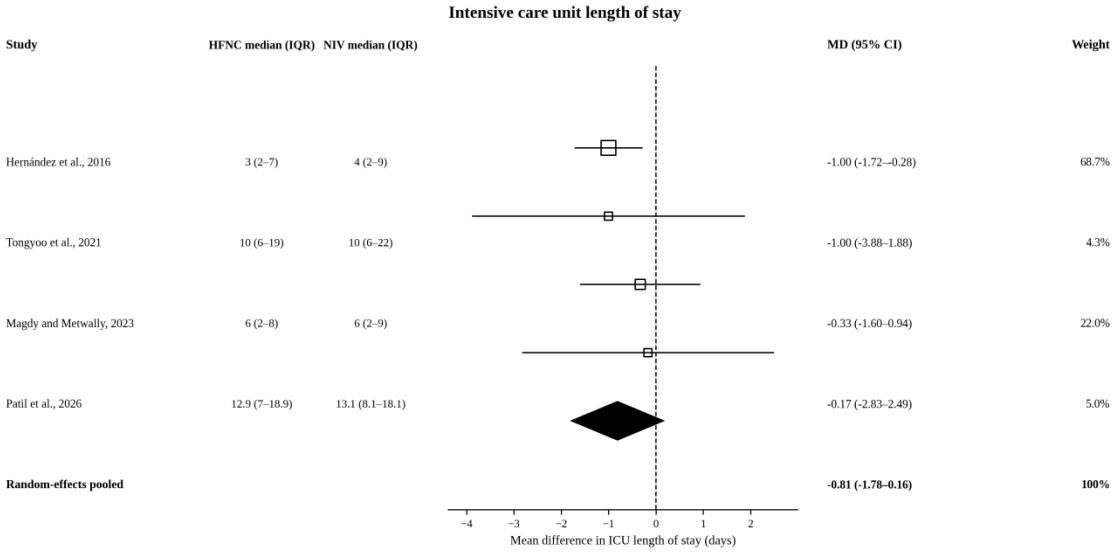

Figure 4: Forest plot of ICU length of stay. Trial medians and interquartile ranges were converted to approximate means and standard deviations

Treatment tolerance and adverse effects

Tolerance outcomes were too inconsistently defined for a defensible pooled estimate. In the 2016 multicenter trial, no HFNC participant required withdrawal because of device-related adverse effects compared with 42.9% in the NIV group [13]. In the 2026 Patil trial, assigned-therapy intolerance occurred in 5/75 HFNC recipients and 17/75 NIV recipients [19].

Prior systematic reviews likewise reported less interface injury and intolerance with HFNC [20]. These findings are clinically important, but they do not prove superior efficacy because inadequate NIV exposure may act as both a mediator and a marker of treatment failure.

Sensitivity Analyses: The common-effect estimate for reintubation was RR 1.08 (95% CI 0.89–1.31), which was more precise but does not adequately represent the observed clinical and statistical heterogeneity. Leave-one-out estimates remained non-significant and ranged from approximately 0.90 to 1.17. Excluding the zero-cell prolonged-ventilation trial yielded RR 0.93 (95% CI 0.49–1.76). Excluding both strongly HFNC-favoring single-center trials (Magdy and Patil) shifted the estimate toward NIV and reduced inconsistency: RR 1.32 (95% CI 0.90–1.95; I^2=18.2%). These changes reinforce that the overall result is sensitive to clinical phenotype and study quality rather than driven by a single trial alone.

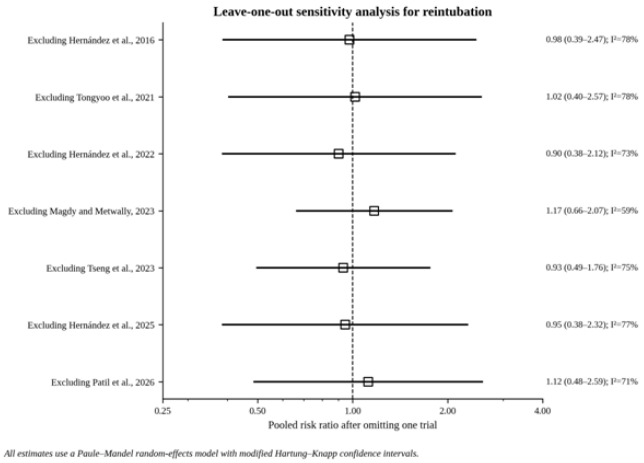

Figure 5: Leave-one-out sensitivity analysis for the primary reintubation outcome

Publication bias and small-study effects: The funnel plot was visually heterogeneous rather than clearly asymmetric. Egger regression yielded an intercept of -0.49 (p=0.812). Because only seven studies were available, this analysis has low power, is vulnerable to genuine effect modification, and cannot exclude publication bias. The extreme effects observed in small single-center trials may reflect chance, protocol differences, selective reporting, or true phenotype-specific treatment effects.

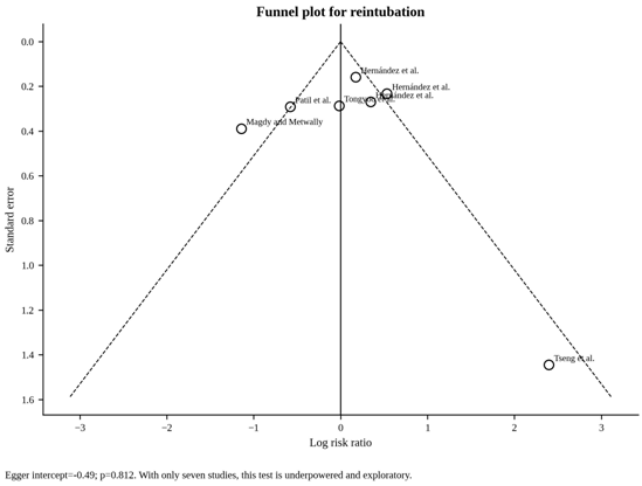

Figure 6: Exploratory funnel plot for reintubation. Formal asymmetry tests are unreliable with fewer than 10 studies

Discussion

This evidence reconstruction found no clear average difference between HFNC and NIV for early reintubation, but the pooled RR of 1.00 conceals substantial and clinically meaningful inconsistency. The primary confidence interval was broad and compatible with benefit from either strategy. By contrast, HFNC was associated with less post-extubation respiratory failure in the subset of trials with extractable compatible data, while mortality and ICU length of stay did not differ reliably.

The most important interpretation is therefore not that HFNC and NIV are equivalent. Rather, the comparative effect appears conditional on patient phenotype and treatment protocol. Trials of actively humidified NIV in very-high-risk or obese patients tended to favor NIV, whereas some trials using shorter, passive-humidified, or potentially less-tolerated NIV protocols favored HFNC. The effect of a device cannot be separated from the delivered dose, interface, humidification, staff expertise, adherence, and escalation policy.

The lower rate of post-extubation respiratory failure with HFNC is biologically plausible. Continuous heated humidification can improve secretion clearance and comfort, while high flow reduces upper-airway dead-space rebreathing and provides a modest expiratory pressure. Better tolerance may permit more continuous support. However, a reduction in a syndrome-level respiratory-failure endpoint did not translate into a consistent reduction in reintubation, possibly because crossover, rescue NIV, clinician thresholds, and non-respiratory indications for reintubation diluted the relationship.

The findings are broadly consistent with the 2023 meta-analysis by Wang et al., which found no significant difference in reintubation or mortality but fewer adverse effects with HFNC [20]. A 2022 network meta-analysis concluded that both HFNC and NIV reduce reintubation compared with conventional oxygen, without a clear direct difference between them [21]. The 2026 systematic review with trial sequential analysis pooled 10 randomized trials and reported no overall difference in reintubation, ICU or hospital mortality, or length of stay, while identifying substantial heterogeneity for reintubation [22]. The present reconstruction reaches a similar high-level conclusion but produces wider uncertainty because it restricts quantitative analyses to directly extractable event counts and uses a small-sample random-effects interval.

Recent trial-level evidence sharpens the risk-based interpretation. The 2022 very-high-risk trial showed fewer reintubations with actively humidified NIV [15], and the 2025 obesity trial showed a non-significant numerical advantage for NIV with Bayesian probabilities favoring benefit [18]. Conversely, the 2026 Patil trial reported lower reintubation with HFNC than with passively humidified NIV [19]. These apparently conflicting findings may be reconciled by differences in NIV quality, humidification, adherence, baseline hypercapnia, obesity, number of risk factors, and endpoint timing.

The 2026 American Thoracic Society guideline adopted a risk-based approach, suggesting HFNC for lower-risk patients and NIV for high-risk patients after extubation [32]. That recommendation is compatible with the present synthesis, provided "high risk" is not treated as a single homogeneous category. Patients with hypercapnia, obesity-related load, chronic respiratory disease, heart failure, or multiple risk factors may derive greater physiological benefit from positive-pressure support, whereas patients without a strong ventilatory indication may prioritize comfort and secretion management.

The leave-one-out analysis showed that no single trial alone converted the pooled result into a precise, significant benefit. Nevertheless, excluding the two strongly HFNC-favoring single-center studies shifted the point estimate toward NIV and substantially reduced heterogeneity. This pattern suggests that protocol and setting effects may be more important than random sampling variation alone. The small number of studies precluded reliable meta-regression; consequently, apparent differences by humidification, phenotype, or risk burden should be viewed as hypothesis-generating rather than causal subgroup effects.

Blinding is impractical in device trials, and reintubation remains partly clinician-dependent despite protocolized criteria. Differential tolerance may lead to treatment crossover or reduced NIV exposure, while knowledge of allocation can affect rescue decisions. The largest HFNC benefits were reported in open-label single-center trials, raising concern about performance bias, center effects, or selective reporting. Conversely, the two Spanish active-humidification trials were relatively rigorous but were not individually definitive. Funnel-plot analysis did not show statistical evidence of asymmetry, but the small number of trials and genuine clinical heterogeneity make absence of statistical significance uninformative. A practical interpretation is to select support according to the mechanism and risk of failure rather than device availability alone. NIV should generally be favored when substantial ventilatory assistance or positive pressure is expected to be beneficial, including marked hypercapnia, obesity-related respiratory load, cardiogenic pulmonary edema, chronic respiratory disease with difficult weaning, or accumulation of multiple risk factors. Active humidification, careful interface fitting, protocolized pressures, scheduled breaks, and close bedside coaching are essential to deliver an adequate NIV dose. HFNC is reasonable for patients at lower or intermediate risk, those with predominantly hypoxemic physiology, secretion-management needs, or poor NIV tolerance. HFNC can also be used during breaks from NIV in selected protocols, although combination strategies were outside the direct comparison in this analysis. Regardless of the initial modality, clinicians should define objective failure and escalation criteria before extubation. Worsening work of breathing, altered mental status, refractory hypoxemia, progressive acidosis or hypercapnia, hemodynamic instability, or inability to clear secretions should prompt immediate reassessment. Neither HFNC nor NIV

should delay reintubation when invasive support is indicated.

Strengths of this model include explicit effect direction, study-level event reconstruction, separate forest plots for each outcome, random-effects inference with small-sample adjustment, leave-one-out analysis, and transparent acknowledgement of heterogeneity and data conversions. The manuscript also incorporates recent trials and the 2026 guideline context. The principal limitation is that this is not a de novo, prospectively registered, independently screened systematic review. Only outcomes with publicly extractable aggregate data were pooled, so the dataset is smaller than some published reviews. Reintubation and respiratory-failure windows differed, mortality follow-up was heterogeneous, and ICU length-of-stay data required approximate conversion from skewed summaries. Some studies enrolled highly selected phenotypes, limiting generalizability. Provisional risk-of-bias judgements were not duplicated. Individual-patient data were unavailable, preventing reliable interaction analyses by hypercapnia, obesity, duration of ventilation, or number of risk factors. Publication-bias methods were underpowered. These limitations preclude definitive claims of equivalence or superiority.

Future multicenter trials should use harmonized 72-hour and 7-day reintubation endpoints, standardized definitions of post-extubation respiratory failure, blinded outcome adjudication where feasible, and protocolized rescue criteria. NIV trials should report active humidification, interface, pressures, delivered hours, intolerance, and crossover in detail; HFNC trials should report flow, temperature, FiO_2, and adherence. Stratification or interaction testing should focus on hypercapnia, obesity, cardiac failure, chronic respiratory disease, inspiratory effort, secretion burden, and cumulative risk factors. Individual-patient-data meta-analysis may be the most efficient route to identifying treatment-responsive phenotypes. Patient comfort, dyspnea, communication, sleep, skin injury, resource use, and cost-effectiveness should be treated as core outcomes rather than ancillary observations.

Conclusion

In adults receiving prophylactic support after planned extubation, HFNC and NIV showed no clear average difference in reintubation, but the evidence was highly heterogeneous and imprecise. HFNC was associated with less post-extubation respiratory failure in the subset of trials with compatible data and is generally better tolerated. Actively humidified NIV may be more effective in very-high-risk, obese, hypercapnic, or otherwise positive-pressure-responsive patients. The evidence supports individualized, protocol-driven selection rather than a universal preference, with close monitoring and timely reintubation when non-invasive support fails.

Declarations

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