

Impact of High-Flow Nasal Cannula for Chronic Obstructive Pulmonary Disease Exacerbation: A Systematic Review of Clinical and Physiological Outcomes

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Background: Chronic obstructive pulmonary disease (COPD) caused 3.72 million deaths in 2021. Exacerbations drive morbidity and hospital admissions. Conventional oxygen therapy (COT) offers limited support, while non-invasive ventilation (NIV) improves outcomes but is often poorly tolerated. High-flow nasal cannula (HFNC) delivers heated, humidified oxygen at high flow rates, improving gas exchange and comfort. This systematic review (PRISMA-guided) examines HFNC use in acute and chronic hypercapnic COPD compared with COT and NIV.

Methods: Systematic searches of MEDLINE, Embase and CENTRAL (to 2025) identified 14 primary studies (7 randomized trials, 7 observational cohorts). Physiological, clinical and patient-reported outcomes were extracted. Risk of bias was evaluated using RoB 2 and ROBINS-I.

Results: In acute settings, HFNC consistently improved PaCO₂ and reduced respiratory effort versus COT, lowering treatment failure (10.0% vs 19.4%, p=0.026). However, HFNC failed non-inferiority versus NIV for treatment failure (25.7% vs 14.3%) and showed higher intubation (14.2% vs 5.4%, p=0.026). Domiciliary HFNC reduced annual exacerbations and improved quality of life (SGRQ mean difference -8.12).

Conclusion: HFNC provides physiological benefits and lowers short-term failure versus COT and reduces home exacerbations. However, it is less effective than NIV for severe hypercapnic failure. HFNC should be reserved for mild-to-moderate exacerbations or NIV-intolerant patients, with close monitoring and predefined escalation criteria.

Keywords: chronic obstructive pulmonary disease, high-flow nasal cannula, non-invasive ventilation, conventional oxygen therapy, exacerbations, hypercapnic respiratory failure

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading global cause of death and disability. The Global Burden of Disease Study estimated 3.72 million COPD-related deaths in 2021, with an age-standardized mortality rate of 45.2 per 100,000 persons.¹ Exacerbations—acute episodes of worsening respiratory symptoms requiring additional treatment—occur approximately 2.4 times per year and are strongly linked to lung function decline and poor quality of life.² Hospitalization for an acute exacerbation carries a one-year mortality approaching 40% when mechanical ventilation is required, rising to 49% by three years.³

Standard respiratory support relies on low-flow conventional oxygen therapy (COT) and non-invasive ventilation (NIV). Low-flow oxygen often fails to meet inspiratory demand, whereas NIV, though effective in reducing intubation and mortality, is frequently limited by patient intolerance.⁴ Current guidelines from GOLD recommend NIV as first-line ventilatory support for acute hypercapnic respiratory failure, but do not endorse HFNC as a replacement.⁴

High-flow nasal cannula (HFNC) therapy has emerged as an alternative, delivering heated, humidified oxygen at flow rates up to 60 L/min with precise FiO_2 control.⁵ HFNC can flush anatomical dead space, reduce CO_2 rebreathing, generate mild positive airway pressure (approximately 2–5 cmH_2O), and ease breathing effort.^{6–8} Despite these physiological benefits, evidence remains mixed: while studies show improved gas exchange and comfort, benefits for intubation, treatment failure, or mortality are inconsistent.^{9,10} A clear knowledge gap exists regarding whether HFNC can safely replace NIV in acute settings or should be reserved for specific subgroups.

This review examines the current evidence for HFNC in COPD exacerbations across three distinct settings: (1) acute in-hospital hypercapnic exacerbations, (2) post-extubation support, and (3) chronic domiciliary use. We focus on its clinical efficacy, safety, and comparative role alongside COT and NIV, with explicit attention to patient severity—mild-to-moderate versus severe hypercapnic respiratory failure—as outcomes differ substantially across these groups.

Methodology

Search Strategy and Selection

A structured literature search was conducted across MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) through 2025. The full search strategy with Boolean operators and controlled vocabulary was as follows: (“high-flow nasal cannula” OR HFNC OR “nasal high flow” OR “heated humidified high-flow nasal cannula”) AND (“COPD exacerbation” OR “acute exacerbation of COPD” OR AECOPD OR “chronic obstructive pulmonary disease” OR “hypercapnic respiratory failure”) AND (“non-invasive ventilation” OR NIV OR “oxygen therapy” OR “conventional oxygen therapy” OR COT OR “post-extubation” OR “domiciliary oxygen”). Reference lists of identified papers were screened to capture additional relevant studies. Preprint servers were not included in this search.

Eligibility Criteria

Included reports comprised randomized controlled trials, randomized crossover physiologic studies, and prospective or retrospective observational cohorts examining HFNC in acute or chronic hypercapnic COPD. Eligible comparisons included NIV or COT. Studies without quantifiable outcomes or original data (eg, case reports, editorials, systematic reviews, meta-analyses, device descriptions) were excluded (Figure 1).

Data Extraction

Two reviewers independently extracted prespecified fields: study design, setting, sample size, inclusion criteria, HFNC settings, comparator, follow-up and quantitative outcomes (PaCO_2 , pH, intubation, treatment failure, length of stay, exacerbation rate, quality of life). Discrepancies were resolved by consensus (Table 1).

Risk of Bias Assessment

Design-appropriate tools were applied. Randomized trials were evaluated using Cochrane RoB 2, crossover trials with RoB 2-crossover, and non-randomized studies with ROBINS-I. Each study received a global judgment as low, some concerns, moderate, serious, or high risk of bias (Table 2).

Data Synthesis and Analysis

Given heterogeneity in disease severity, HFNC protocols and comparators, formal meta-analysis was not performed. Reported pooled estimates from existing reviews are summarized. Studies were stratified by setting: (1) acute in-hospital COPD exacerbation, (2) post-extubation support, and (3) domiciliary long-term therapy. Quantitative emphasis was placed on direction and magnitude of physiological change (PaCO_2 , respiratory rate, end-expiratory lung volume [EELV]) and on clinically relevant outcomes: treatment failure, intubation, and exacerbation frequency. Sensitivity appraisal prioritized randomized evidence and crossover physiology studies (Table 3).

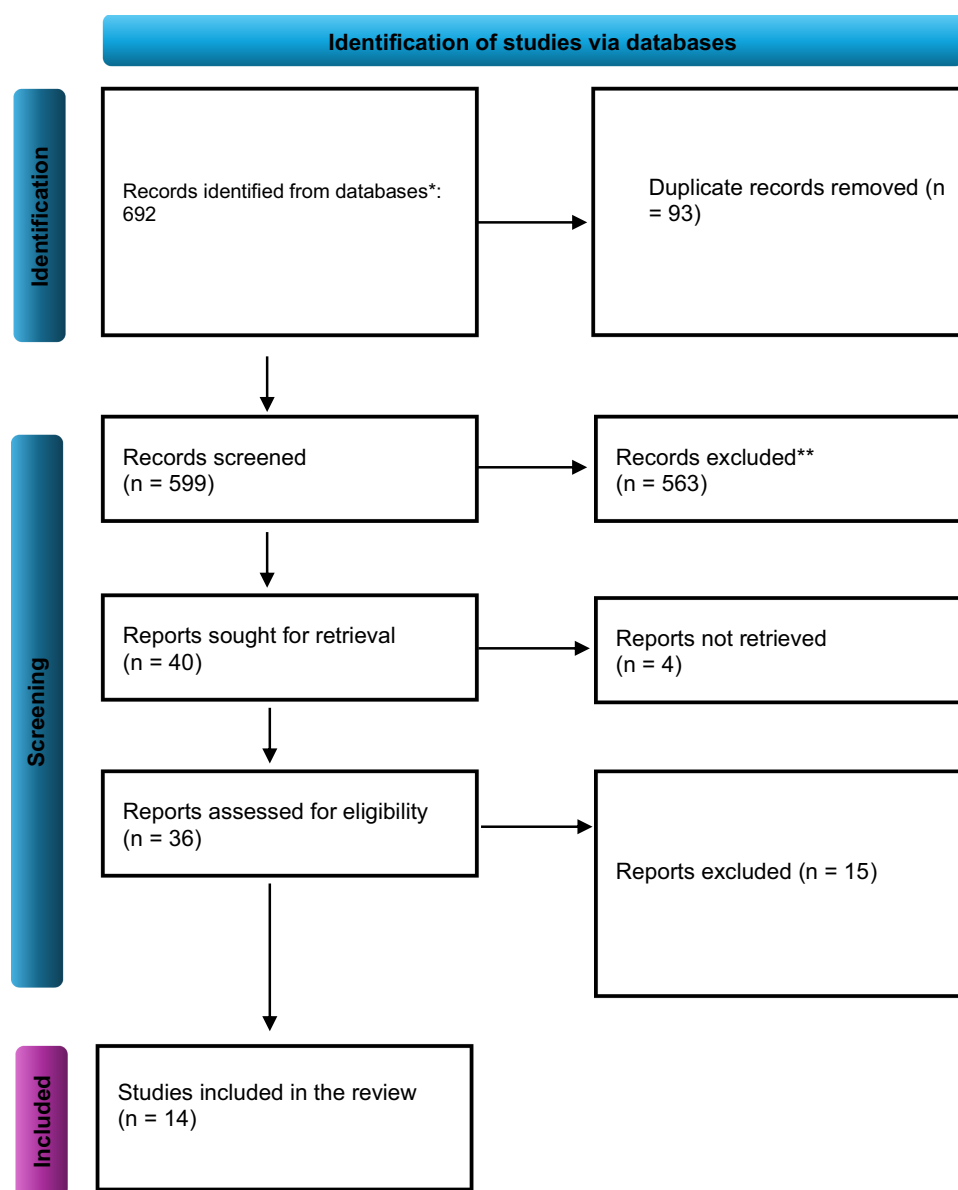


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the studies' selection process.

Notes: This figure was adapted from Page, Matthew J., et al "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews". *bmj* 372 (2021). <https://doi.org/10.1136/bmj.n71>. * The studies were identified from the databases. ** The studies were excluded after the initial screening.

Methodological Limitations

Open-label designs, short follow-up intervals, and heterogeneous HFNC settings limit causal interpretation. Observational data are subject to confounding by indication, while underpowered RCTs constrain precision. These weaknesses informed a conservative synthesis and highlight the need for larger, protocol-standardized multicenter trials.

Results

Across fourteen studies, seven were randomized or crossover trials and seven observational (Table 1). Sample sizes ranged from small physiologic groups ($n=10$) to large multicenter trials ($n>300$). Most studies addressed acute or post-extubation hypercapnic COPD, while a smaller group examined long-term domiciliary use. Only two small physiologic trials met a low risk-of-bias standard. The larger randomized studies were often open-label, short in duration, and statistically underpowered. Observational work suffered from selection effects and inconsistent reporting.

Table 1 Characteristics of Included Studies on High-Flow Nasal Cannula (HFNC) in COPD Exacerbation

#	Citation	Year	Design	Population (n)	Intervention	Comparator	Physiologic Outcomes (Direction of Effect)	Clinical Outcomes (Direction of Effect)	RoB Judgment
1	Cortegiani et al ¹¹	2020	RCT non-inferiority	79	HFNC	NIV	↓PaCO ₂ (non-inferior)	↑NIV escalation (32% by 6h)	Some concerns
2	Xia et al ¹²	2022	RCT	330	HFNC	COT	↓PaCO ₂	↔Intubation; ↑LOS	High
3	Nagata et al ¹³	2022	RCT domiciliary	104	HFNC+LTOT	LTOT	↓PaCO ₂	↓Exacerbations; ↑QoL	Some concerns
4	Di Mussi et al ¹⁴	2018	Crossover	≈14	HFNC	Standard O ₂	↓Neuroventilatory drive; ↓WOB	Not reported	Some concerns
5	Fraser et al ¹⁵	2016	Crossover	30	HFNC	Baseline	↓RR; ↓TcCO ₂ ; ↑Vt; ↑EELV	Not reported	Low
6	Braunlich et al ¹⁶	2018	Observational	Small cohorts	HFNC	Baseline	↓PaCO ₂ (flow-dependent)	Not reported	Moderate
7	Sun J. et al ¹⁷	2019	Observational cohort	82	HFNC	NIV	Not reported	↔Treatment failure; ↓Skin breakdown	Moderate
8	Veenstra et al ¹⁸	2022	Retrospective cohort	69	HFNC	None	Not reported	61% clinical success	Moderate
9	Nam K-H. et al ¹⁹	2021	Prospective obs	45	HFNC	Before/after	↓PaCO ₂ (3.8 mmHg)	6.7% escalation	Moderate
10	Kuo Y-L. et al ²⁰	2022	Crossover	Small	HFNC	Nasal cannula	↓Respiratory impedance	Not reported	Low
11	Storgaard LH. et al ²¹	2018	Longitudinal obs	200	HFNC+LTOT	LTOT	↓PaCO ₂ at 12 mo	↓Exacerbations (3.12 vs 4.95)	Serious
12	Tan D. et al ²²	2020	RCT non-inferiority	225	HFNC	NIV	↓PaCO ₂ (inferior to NIV)	↑Treatment failure; ↑Intubation	Some concerns
13	Zhong Z. et al ²³	2025	Meta-analysis (9 RCTs)	786	HFNC	NIV	Not applicable	↔Mortality; ↑Treatment failure (trend)	Serious
14	Li X-Y. et al ⁴	2023	RCT	320	HFNC	COT	↓PaCO ₂ at 24h	↓Treatment failure (10% vs 19.4%)	Low

Notes: ↓ = decrease/improvement; ↑ = increase/worsening; ↔ = no significant difference.

Abbreviations: RCT, randomized controlled trial; HFNC, high-flow nasal cannula; NIV, non-invasive ventilation; COT, conventional oxygen therapy; LTOT, long-term oxygen therapy; LOS, length of stay; QoL, quality of life; WOB, work of breathing; RR, respiratory rate; TcCO₂, transcutaneous carbon dioxide; Vt, tidal volume; EELV, end-expiratory lung volume; mo, months; h, hours; obs, observational.

Table 2 Risk of Bias of Included Studies (n=14)

Study (First Author, Year)	Design	Risk-of-Bias Tool	Overall Judgment
Cortegiani A. (2020) ¹¹	Multicenter RCT (non-inferiority)	RoB 2	Some concerns
Xia J. (2022) ¹²	Multicenter RCT	RoB 2	High
Nagata K. (2022) ¹³	Home-based RCT	RoB 2	Some concerns
Di Mussi R. (2018) ¹⁴	Randomized crossover	RoB 2-crossover	Some concerns
Fraser J. F. (2016) ¹⁵	Randomized crossover	RoB 2-crossover	Low
Braunlich J. (2018) ¹⁶	Observational (physiologic)	ROBINS-I	Moderate
Sun J. (2019) ¹⁷	Observational cohort	ROBINS-I	Moderate
Veenstra P. (2022) ¹⁸	Retrospective cohort	ROBINS-I	Moderate
Nam K-H. (2021) ¹⁹	Prospective observational	ROBINS-I	Moderate
Kuo Y-L. (2022) ²⁰	Randomized crossover	RoB 2-crossover	Low
Storgaard L. H. (2018) ²¹	Longitudinal observational	ROBINS-I	Serious
Tan D. (2020) ²²	Randomized non-inferiority trial	RoB 2	Some concerns
Zhong Z. (2025) ²³	Meta-analysis of RCTs	ROBINS-I	Serious
Li X-Y. (2023) ⁴	Randomized controlled trial	RoB 2	Low

Table 3 Primary Findings of Selected Studies

#	Citation (First Author, Year)	Reported n	Main Numeric Results
1	Xia J., Gu S., Lei W., et al ¹²	330 completed	Intubation criteria: 4/158 (2.5%) HFNC vs 1/172 (0.6%) COT, p=0.198. Treatment escalation to NIV: 15/158 (9.5%) vs 22/172 (12.8%), p=0.343. Median LOS: 9 vs 8 days.
2	Nagata K., Horie T., et al ¹³	104	Moderate/severe exacerbations (52 wk): mean 1.0±1.8 (HFNC+LTOT) vs 2.5±3.8 (LTOT alone), adjusted ratio 2.85 (95% CI 1.48–5.47), p=0.002.
3	Li X-Y., Tang X., Wang R., et al ⁴	320	Treatment failure: 16/160 (10.0%) HFNC vs 31/160 (19.4%) COT, p=0.026. PaCO ₂ at 24h: 54.1±9.79 vs 56.9±10.1 mmHg, p=0.030.
4	Di Mussi R., et al ¹⁴	≈14 crossover	EAdiPEAK: 15.4±6.4 μV (HFNC) vs 23.6±10.5 μV (COT), p<0.05. PTPdi/min: 135±60 vs 211±70 cmH ₂ O s/min, p<0.05.
5	Fraser JF, et al ¹⁵	30	TcCO ₂ : 43.3 vs 46.7 mmHg, p<0.001. RR: 15.4 vs 19.2 bpm, p<0.001. Vt: 0.50 vs 0.40 L, p=0.003.
6	Cortegiani A., et al ¹¹	79 analyzed	ΔPaCO ₂ at 2h: -6.8±8.7 mmHg (HFNC) vs -9.5±8.5 mmHg (NIV), difference 2.7 mmHg (1-sided 95% CI upper bound 6.1), p for non-inferiority=0.0003. 32% HFNC→NIV by 6h.
7	Tan D., et al ²²	225 ITT	Treatment failure: 25.7% HFNC vs 14.3% NIV, risk difference 11.38% (95% CI 0.25–21.20), p=0.033. Intubation: 14.2% vs 5.4%, p=0.026.
8	Storgaard LH., et al ²¹	200	AECOPD rate: 3.12 vs 4.95 events/patient-year, p<0.001. Hospital admissions: 0.79 vs 1.39/patient-year, p<0.001. PaCO ₂ reduction at 12 mo: p=0.005.

Abbreviations: HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; NIV, non-invasive ventilation; LTOT, long-term oxygen therapy; LOS, length of stay; ITT, intention-to-treat; EAdi, electrical activity of the diaphragm; PTPdi, pressure-time product of the diaphragm; TcCO₂, transcutaneous carbon dioxide; RR, respiratory rate; Vt, tidal volume; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CI, confidence interval.

Acute In-Hospital Studies: Physiologic Outcomes

High-flow nasal cannula (HFNC) shows consistent short-term physiologic benefit in COPD. Physiologic trials report reproducible reductions in CO₂ and work of breathing. In a randomized crossover trial, Fraser et al¹⁵ found transcutaneous CO₂ decreased from 46.7 to 43.3 mmHg (p<0.001), respiratory rate fell from 19.2 to 15.4 breaths per minute (p<0.001), tidal

volume rose from 0.40 to 0.50 L ($p=0.003$), and EELV increased markedly ($p<0.001$). Di Mussi et al¹⁴ showed neuroventilatory drive (EAdi peak) fell from 23.6 ± 10.5 μ V to 15.4 ± 6.4 μ V and PTPdi/min fell from 211 ± 70 to 135 ± 60 cmH₂O·s/min ($p<0.05$ for both).

Acute In-Hospital Studies: Clinical Outcomes

Clinical trials produce heterogeneous results that hinge on setting and patient severity. In controlled comparisons versus COT, Li et al⁴ reported reduced treatment failure at 24 hours with HFNC (16/160 [10.0%] versus COT 31/160 [19.4%], $p=0.026$) and lower PaCO₂ at 24 hours (54.1 ± 9.79 vs 56.9 ± 10.1 mmHg, $p=0.030$). Xia et al¹² enrolling patients with milder hypercapnia, found no significant reduction in intubation criteria during hospitalization (4/158 versus 1/172, $p=0.198$), and HFNC was associated with longer median length of stay (9 vs 8 days).

Comparisons with Non-Invasive Ventilation

Comparisons with NIV show caution is necessary. Cortegiani et al¹¹ met a physiological non-inferiority margin for PaCO₂ at two hours. Mean Δ PaCO₂ was -6.8 ± 8.7 mmHg with HFNC versus -9.5 ± 8.5 mmHg with NIV. The absolute difference (2.7 mmHg) satisfied the prespecified non-inferiority bound (p for non-inferiority = 0.0003), but 32% of HFNC patients switched to NIV by six hours. Tan et al²² produced a larger randomized dataset. Treatment failure occurred in 25.7% with HFNC versus 14.3% with NIV. The risk difference (11.38%, 95% CI 0.25 to 21.20, $p=0.033$) exceeded the non-inferiority margin, so HFNC failed to demonstrate non-inferiority. Intubation rates were higher with HFNC (14.2% versus 5.4% with NIV, $p=0.026$).

Domiciliary HFNC

Domiciliary HFNC yields more consistent clinical advantages for chronic hypercapnic COPD. Nagata et al¹³ and Storgaard et al²¹ reported reduced exacerbation rates and improved quality of life (St. George's Respiratory Questionnaire [SGRQ] mean difference -8.12 , 95% CI -13.30 to -2.95). The meta-analysis by Pitre et al²⁴ confirmed a pooled relative risk reduction in exacerbations (RR 0.77, 95% CI 0.66–0.89) and improvements in dyspnoea indices.

Discussion

The current body of evidence on HFNC in acute exacerbations of COPD (AECOPD) reveals a field in transition—from physiologic promise to cautious clinical application. Physiological studies consistently support HFNC's capacity to improve ventilation mechanics, reduce inspiratory effort, and enhance carbon dioxide clearance compared with COT.^{14,15} The consistent reduction in transcutaneous CO₂, diaphragmatic pressure-time product, and respiratory rate observed in crossover studies^{14,15} confirms that high-flow nasal cannula generates meaningful physiological unloading. These improvements are not merely statistical; the increased end-expiratory lung volume and reduced neuroventilatory drive indicate effective counteraction of dynamic hyperinflation, the core pathophysiological defect in acute exacerbations of COPD. By flushing anatomical dead space and providing low-level positive pressure, high-flow nasal cannula reduces the work of breathing at a level detectable by both electrical diaphragmatic activity and ventilatory pattern analysis, establishing a clear mechanistic rationale for clinical application. Short physiologic crossover trials provide a controlled signal supporting HFNC's mechanistic effect. In randomized crossover settings, where each patient serves as their own control, HFNC consistently reduced transcutaneous CO₂, respiratory rate, and diaphragmatic effort within hours of application.^{14,15} These short-duration studies isolate device-specific effects from disease variability and confirm that the observed improvements in ventilation and work of breathing are directly attributable to high-flow therapy rather than clinical progression. However, their brief time horizon and small sample sizes limit extrapolation to sustained clinical outcomes such as intubation or mortality, reinforcing that physiologic benefit alone is insufficient to establish equivalence with NIV in more severe exacerbations.

Despite these mechanistic advantages, the translation to clinically significant outcomes is inconsistent. Meta-analyses demonstrate modest mean PaCO₂ reduction and a reduction in treatment failure versus COT, yet they fail to show meaningful benefit in mortality or intubation.^{12–19,24–26} The lack of statistical difference despite physiologic improvement suggests that HFNC is most effective in borderline cases—patients with mild hypercapnia or moderate exacerbations who do not yet need ventilatory assistance.⁴

In contrast, when compared with NIV, HFNC demonstrates both its clinical limits and its patient-centered strengths. NIV remains superior for controlling hypercapnia and preventing intubation in moderate to severe exacerbations.²² Data demonstrate that HFNC's physiologic benefit does not equate to ventilatory efficacy. NIV remains the intervention of choice for acute hypercapnic respiratory failure, while HFNC serves as a comfort-oriented adjunct, suitable when NIV is contraindicated, poorly tolerated, or being weaned.¹¹

Comfort, tolerance, and patient interface outcomes are consistently superior with HFNC. Yang et al²⁵ found that HFNC reduced interface-related skin breakdown by nearly half compared with NIV (RR 0.52, 95% CI 0.39–0.69). Sun et al¹⁷ corroborated this, reporting fewer airway interventions and lower rates of pressure injury with HFNC. Improved tolerance allows longer continuous use, potentially stabilizing patients who would otherwise fail COT. However, this comfort advantage must be weighed against delayed escalation risk—patients may appear clinically stable while ventilation deteriorates.

Beyond acute management, HFNC demonstrates a more consistent role in chronic or domiciliary settings. Long-term studies indicate that nightly HFNC use reduces the frequency of moderate and severe exacerbations and improves quality-of-life scores.^{13–21,24–26} The chronic benefit likely arises from sustained washout of anatomical dead space, reduced CO₂ retention during sleep, and improved mucociliary clearance—mechanisms less dependent on immediate ventilatory drive.^{27–29}

Limitations

Several limitations must be acknowledged. At the study level, most included trials had small sample sizes, short follow-up durations (often 24–72 hours for acute studies), and heterogeneous HFNC settings (flow rates ranging 30–60 L/min, variable FiO₂ titration protocols). Open-label designs are common due to the inability to blind patients and clinicians to device type, introducing performance bias. Observational studies are subject to confounding by indication, where sicker patients may preferentially receive NIV. At the review level, we did not perform a meta-analysis due to substantial clinical and methodological heterogeneity across studies. Furthermore, the absence of standardized outcome definitions—particularly for “treatment failure” and “escalation criteria”—limits comparability across trials. Ongoing controversies remain regarding optimal patient selection, flow titration protocols, and long-term safety, which await resolution in larger, adequately powered multicenter RCTs.

Conclusion

In summary, HFNC holds a defined but selective place in COPD management. It is superior to COT for mild-to-moderate exacerbations, offering physiological relief and improved comfort. It does not, however, match the efficacy of NIV in severe hypercapnic episodes and should not be used as its substitute in that context. Safety considerations require close monitoring of PaCO₂ and work of breathing, with predefined escalation criteria to prevent delayed intubation. Its most promising role appears to be in domiciliary therapy for stable, chronically hypercapnic COPD, where it meaningfully reduces exacerbations and improves patient well-being. Further large-scale randomized trials are needed to identify patient profiles that benefit most and to standardize its application in both acute and chronic settings.

Disclosure

The authors report no conflicts of interest in this work.

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