Cureus
Part of SPRINGER NATURE

Open Access Review Article

Efficacy of High-Velocity Nasal Insufflation in the Treatment of Hypercapnic Respiratory Failure: A Systematic Review and Meta-Analysis

Shunsuke Kondo [1, 2], Collin R. Clarke [1], Joshua J. Garcia [1], Yuki Kataoka [3, 4, 5, 6, 7, 8], Brent J. Matsuda [9, 10]

1. Department of Internal Medicine, University of Hawai'i John A. Burns School of Medicine, Honolulu, USA 2. Department of Research, Scientific Research WorkS Peer Support Group, Osaka, JPN 3. Department of Systematic Reviewers, Scientific Research Works Peer Support Group, Osaka, JPN 4. Department of Healthcare Epidemiology, Kyoto University Graduate School of Medicine/School of Public Health, Kyoto, JPN 5. Center for Postgraduate Clinical Training and Career Development, Nagoya University Hospital, Nagoya, JPN 6. Center for Medical Education, Graduate School of Medicine, Nagoya University, Nagoya, JPN 7. Department of International and Community Oral Health, Tohoku University Graduate School of Dentistry, Sendai, JPN 8. Department of Internal Medicine, Kyoto Min-iren Asukai Hospital, Kyoto, JPN 9. Department of Medicine, University of Hawai'i John A. Burns School of Medicine, Honolulu, USA 10. Division of Pulmonary and Critical Care, Department of Medicine, The Queen's Medical Center, Honolulu, USA

Corresponding author: Shunsuke Kondo, h26ms.kondo@gmail.com

Review began 10/05/2026
Review ended 10/26/2026
Published 10/30/2026

© Copyright 2026
Kondo et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.118857

Abstract

High-velocity nasal insufflation (HVNI) is a nasal cannula-based respiratory support modality that may offer an alternative interface to noninvasive positive-pressure ventilation (NPPV). However, randomized evidence specific to HVNI in acute hypercapnic respiratory failure remains limited.

We conducted a systematic review and meta-analysis of randomized controlled trials comparing HVNI with NPPV in adults with acute hypercapnic respiratory failure. MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform were searched initially on August 24, 2025, and updated on October 17, 2026. Prespecified primary outcomes were treatment failure, patient-reported discomfort, time to successful liberation from assisted ventilation, length of stay, and health-related quality of life. Random-effects meta-analyses used DerSimonian-Laird estimation with Hartung-Knapp-adjusted confidence intervals. The protocol was prospectively registered on the Open Science Framework (OSF; by3je).

Four RCTs involving 190 participants were included. HVNI did not show a clear difference in treatment failure compared with NPPV (RR 0.85, 95% CI 0.30-2.45; very low-certainty evidence). Hospital length of stay also showed no clear difference (MD −1.17 days, 95% CI −2.38 to 0.03), and the estimate for ICU length of stay was highly imprecise (MD −0.95 days, 95% CI −6.04 to 4.15). Patient discomfort was reported by one trial and favored HVNI (MD −23.12 points, 95% CI −38.36 to −7.88). No trial reported time to successful liberation from assisted ventilation. Interpretation was limited by the small number and sample sizes of included trials and differences in outcome definitions across studies.

Current evidence is insufficient to determine whether HVNI provides clinically comparable outcomes to NPPV in acute hypercapnic respiratory failure. Additional adequately powered randomized trials are required.

Categories: Pulmonology, Internal Medicine
Keywords: high-flow nasal cannula, moderate respiratory failure, non-invasive mechanical ventilation, patient comfort, pulmonology and critical care

Introduction And Background

Respiratory failure is a common presentation in emergency departments and often requires intensive care management, including endotracheal intubation [1]. Endotracheal intubation is associated with complications and prolonged ICU length of stay. Thus, avoiding intubation through noninvasive therapies can offer meaningful clinical benefits [2,3].

Among noninvasive therapies, noninvasive positive-pressure ventilation (NPPV) is recommended as first-line ventilatory support for selected patients with acute hypercapnic respiratory failure, particularly those with acute exacerbations of chronic obstructive pulmonary disease (COPD) and respiratory acidosis [1,4]. Acute hypercapnic respiratory failure is generally characterized by an elevated $PaCO_2$ with respiratory acidosis; in acute exacerbations of COPD, a pH <7.35 with persistent hypercapnia is commonly used as a threshold for initiating NPPV [1]. Acute hypercapnic respiratory failure complicates approximately 20% of acute COPD exacerbations and is associated with substantial morbidity and mortality [1]. Although NPPV reduces intubation and mortality, treatment failure still occurs in clinical practice; reported NIV failure rates

in patients with acute exacerbations of COPD vary substantially across settings. In a large multicenter observational analysis of patients hospitalized with acute exacerbations of COPD, NIV failure rates ranged from 3.7% to 31.3% across hospitals, with a median of 8.5% [5]. Mask intolerance, impaired communication, limitations on oral intake, and interface-related discomfort may also limit treatment [6].

High-velocity nasal insufflation (HVNI) is a form of high-flow respiratory support delivered through a small-bore nasal cannula. In the randomized trials included in this review, flows were generally initiated at approximately 20-30 L/min and titrated up to 30-40 L/min, with heated humidification and FiO_2 adjusted according to oxygenation targets [7-10]. Compared with conventional large-bore high-flow systems, HVNI uses a narrower cannula and higher gas velocity, characteristics intended to enhance upper-airway dead-space clearance and reduce rebreathing [11,12]. These physiological characteristics provide a rationale for evaluating HVNI as an alternative noninvasive respiratory-support modality in selected patients with acute hypercapnic respiratory failure. Because the interface is nasal rather than mask-based, HVNI may also improve tolerance and facilitate communication and oral intake, although these potential advantages require clinical confirmation [6,13].

Several randomized trials have compared HVNI with NPPV in patients with acute hypercapnic respiratory failure, but the individual studies have been small, and their findings remain uncertain [7-10]. Previous systematic reviews and meta-analyses have evaluated conventional high-flow nasal cannula (HFNC) or broader high-flow nasal therapy compared with NPPV in acute hypercapnic respiratory failure [14-16]. However, these reviews were not specific to HVNI, which differs from conventional high-flow systems in cannula geometry and gas-delivery characteristics. Therefore, the comparative effectiveness of HVNI and NPPV in this population remains uncertain.

Treatment failure was considered a clinically important outcome because failure of noninvasive respiratory support may necessitate escalation of therapy, including endotracheal intubation, and may be associated with adverse clinical outcomes. We therefore sought to synthesize randomized evidence comparing HVNI with NPPV in adults with acute hypercapnic respiratory failure, focusing on treatment failure and other patient-important outcomes.

This work was previously presented as a meeting oral abstract at the 2026 Hawaii Chapter Scientific Meeting of the American College of Physicians on February 28, 2026.

Review

Protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) guidelines when conducting and reporting this review [17]. The PRISMA checklist is shown in Appendix 1. The review protocol was registered prospectively on the Open Science Framework [18].

Eligibility criteria

Eligible studies were selected according to the prespecified inclusion and exclusion criteria summarized in Table *1*.

Domain	Inclusion criteria	Exclusion criteria
Study design	Randomized controlled trials, including individually randomized and cluster-randomized trials	Observational studies and other non-randomized study designs
Participants	Adults aged ≥18 years with acute hypercapnic or type II respiratory failure, as defined by the investigators of the original study. Studies enrolling mixed respiratory-failure populations were eligible when the hypercapnic subgroup was separately reported and subgroup membership was determined using baseline characteristics assessed before treatment allocation. Post-randomization subgroups defined using information obtained after treatment allocation, such as discharge diagnoses, were excluded because of the potential for selection bias.	Participants aged <18 years; studies restricted to hypoxemic/type I respiratory failure; mixed populations from which hypercapnic participants could not be separately evaluated.
Definition of hypercapnic respiratory failure	Acute hypercapnic or type II respiratory failure as defined by the investigators of the original study; no uniform $PaCO_2$ or pH threshold was imposed across studies	Studies not meeting the prespecified definition of acute hypercapnic respiratory failure
Clinical status at presentation	Patients considered appropriate for noninvasive respiratory support	Patients requiring immediate endotracheal intubation at presentation
Cardiorespiratory arrest	Patients without cardiac or respiratory arrest at presentation	Patients presenting with cardiac or respiratory arrest
Intervention	High-velocity nasal insufflation delivered using any initial device settings	Studies not evaluating high-velocity nasal insufflation
Comparator	Noninvasive positive-pressure ventilation, regardless of initial settings or interface	Studies without a noninvasive positive-pressure ventilation comparator
Publication status	Published articles, unpublished studies, conference abstracts, and correspondence articles	None based on publication status
Language	No language restriction	None based on language
Country	No country restriction	None based on country
Publication year	No publication-year restriction	None based on publication year
Follow-up duration	No restriction on follow-up duration	None based on follow-up duration

TABLE 1: Eligibility criteria

Intervention and comparison

The intervention of interest was HVNI delivered via any initial device settings. The comparator was standard care involving NPPV, regardless of initial settings or interface.

Outcomes

We prespecified treatment failure, patient-reported discomfort, time to successful liberation from assisted ventilation, length of stay, and health-related quality of life as primary outcomes. These prespecified outcomes were retained because they represent complementary clinically relevant domains, including failure of the assigned respiratory-support strategy, patient experience, duration of respiratory support, healthcare resource use, and longer-term patient-centered recovery.

In the protocol, treatment failure was defined as the first occurrence of all-cause mortality or unplanned endotracheal intubation. However, this prespecified composite could not be reconstructed consistently from all included trial reports. For the quantitative synthesis, we therefore used the study-defined treatment-

failure outcome reported by each trial; when a trial did not report a composite treatment-failure outcome, we derived the outcome from reported intubation and mortality data when possible. Study-specific definitions and follow-up periods are provided in Table *2*. Because the components of treatment failure differed among trials, the pooled estimate was interpreted as a synthesis of study-defined treatment failure rather than a uniform mortality-or-intubation composite.

Study	Setting and population	Study-specific definition of hypercapnic respiratory failure	Participants included in this review	Baseline PCO_2 and pH	HVNI protocol	NPPV/NIV protocol	Relevant outcome definitions and follow-up
Abd El Aziz et al., 2024 [7]	Single-center chest department, Egypt; mixed acute respiratory failure population. Only the type II respiratory failure subgroup was included in this review.	Type II respiratory failure: pH <7.35, PaO_2 <60 mmHg, and $PaCO_2$ >50 mmHg	28; HVNI 12, NIV 16	HVNI: $PaCO_2$ 63.42 ± 7.16 mmHg; pH 7.33 ± 0.06. NIV: $PaCO_2$ 66.44 ± 8.29 mmHg; pH 7.31 ± 0.064	Precision Flow Plus (Vapotherm); flow 30–40 L/min; temperature 37°C; initial FiO_2 1.0, subsequently adjusted	VIVO 2; BiPAP S/T for hypercapnic RF; backup rate 15/min; initial IPAP 15 cmH_2O and EPAP 5 cmH_2O, increased as needed; initial FiO_2 1.0	ABG assessed at baseline and 2, 6, 12, and 24 h. Treatment failure within 72 h comprised failure of oxygenation, failure of ventilation, clinical deterioration, or intolerance. Hospital LOS and in-hospital mortality were also reported.
Elhofy et al., 2025 [8]	Single-center respiratory ICU, Egypt; adults admitted with acute hypercapnic respiratory failure; COPD was the most common diagnosis	Acute hypercapnic respiratory failure as diagnosed by the investigators; no explicit numeric enrollment threshold was reported in the Methods	48; HVNI 24, NPPV 24	Exact baseline $PaCO_2$ and pH values were not numerically reported; values were presented graphically	Vapotherm Precision Flow; initial flow 25 L/min, increased to 40 L/min; temperature 35–37°C; FiO_2 40%–100% guided by oxygen saturation	Philips Respironics System One 60-series BiPAP Pro Bi-Flex; IPAP 16–20 cmH_2O; EPAP 5–8 cmH_2O; FiO_2 guided by oxygen saturation	ABG assessed at baseline, 1 h, 4 h, day 2, and day 3. Treatment failure was defined as endotracheal intubation or crossover to the alternative therapy. Respiratory support through 72 h, hospital/RICU LOS, in-hospital mortality, and 28-day post-discharge mortality were reported.
Yamane et al., 2025 [9]	Seven U.S. EDs; acute COPD exacerbation with hypercapnic respiratory failure	Blood-gas pCO_2 ≥60 mmHg andvenous pH 7.0–7.35	73 randomized; 68 received allocated treatment and were analyzed: HVNI 36, NiPPV 32	HVNI: pCO_2 77.7 ± 13.6 mmHg; pH 7.27 ± 0.063. NiPPV: pCO_2 76.5 ± 13.6 mmHg; pH 7.27 ± 0.043	Vapotherm; flow 30 L/min; FiO_2 0.50; temperature 37°C; subsequently titrated	FiO_2 0.50; inspiratory pressure 10–12 cmH_2O; expiratory pressure 5–6 cmH_2O; target tidal volume 6–8 mL/kg ideal body weight; subsequently titrated	Assessments at baseline, 30 min, 60 min, and 4 h. Treatment failure included intolerance, failure to oxygenate, failure to ventilate, or clinical deterioration. Dyspnea, intubation, blood gases, and patient discomfort were assessed.
Shaaban et al., 2025 [10]	Single-center respiratory ICU, Egypt; acute exacerbation of COPD–OSA overlap syndrome with hypercapnic respiratory failure	Hypercapnic respiratory failure as diagnosed by the investigators; no separate numeric enrollment threshold was specified	46; HVNI 23, NIV 23	HVNI: $PaCO_2$ 74.09 ± 11.11 mmHg; pH 7.29 ± 0.04. NIV: $PaCO_2$ 76.87 ± 10.92 mmHg; pH 7.27 ± 0.05	Precision Flow Hi-VNI 2000i; initial flow 20 L/min, increased to 30–40 L/min; temperature 37°C; FiO_2 adjusted to target PaO_2 ≥60 mmHg and SaO_2 88%–92%	Puritan-Bennett 840, SIMV-PC; PEEP 6–8 cmH_2O; pressure support 15–20 cmH_2O; rate 12–16/min; FiO_2 adjusted to the same oxygenation targets	ABG assessed at baseline, 24 h, and 48 h. ICU outcomes included intubation, mortality, and complications; ICU LOS was reported for all 46 patients, and hospital LOS for 44 survivors. Review-defined treatment failure was derived from reported intubation and mortality outcomes.

TABLE 2: Characteristics of the included studies

ABG, arterial blood gas; COPD, chronic obstructive pulmonary disease; ED, emergency department; EPAP, expiratory positive airway pressure; FiO_2, fraction of inspired oxygen; HVNI, high-velocity nasal insufflation; ICU, intensive care unit; IPAP, inspiratory positive airway pressure; LOS, length of stay; NIV, noninvasive ventilation; NPPV, noninvasive positive-pressure ventilation; OSA, obstructive sleep apnea; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PCO_2, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; PS, pressure support; RF, respiratory failure; RICU, respiratory intensive care unit; SaO_2, arterial oxygen saturation; SIMV-PC, synchronized intermittent mandatory ventilation-pressure control; S/T, spontaneous/timed; VAS, visual analog scale.

The protocol termed this outcome “perception of comfort.” In this manuscript, we report the outcome as patient-reported discomfort to reflect the direction of the scale used in the included trial. Patient-reported

discomfort was assessed using a 0-100 visual analog scale (VAS), with lower scores indicating less discomfort. The protocol prespecified extraction at the time point closest to 72 hours; however, the only available continuous discomfort assessment was reported at four hours, as described under Differences between protocol and review. Time to successful liberation from assisted ventilation was defined as the time from randomization to the first episode of at least 48 hours of unassisted breathing or to death. Hospital and ICU length of stay were collected separately.

Health-related quality of life was extracted as reported by the original investigators.

Secondary outcomes included failure to oxygenate, failure to ventilate, and adverse events. Failure to oxygenate was defined as the inability to maintain oxygen saturation > 88% or partial pressure of oxygen > 60 mm Hg despite treatment with 100% FIO2 and optimal manipulations of flow rate and airway pressure, while failure to ventilate referred to remain hypercapnic with PaCO2 ⩾60 mmHg and acidemic with pH between 7.0 and 7.35, with analyses restricted to participants who had baseline hypercapnia. Adverse events were summarized descriptively according to definitions provided in the original studies, and no meta-analysis was performed for this outcome.

For outcomes reported by only one study, we did not perform a meta-analysis. Instead, we presented the study-specific effect estimate with its 95% confidence interval (CI) and assessed the certainty of the evidence using the GRADE approach. Prespecified critical and important outcomes were retained in Table *3* regardless of whether meta-analysis was possible.

HVNI compared to NPPV for acute hypercapnic respiratory failure

Patient or population: acute hypercapnic respiratory failure; Setting: Intervention: HVNI Comparison: NPPV

Outcome: no. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		NPPV	HVNI	Difference		
Treatment failure: no. of participants: 190 (4 RCTs)	RR 0.85 (0.30–2.45)	20.00%	17.00%	3.0% fewer (14.0 fewer to 29.0 more)	□◯◯◯ Very low[a,b]	
Patient-reported discomfort (VAS, 0–100; lower scores indicate less discomfort) No of participants: 55 (1 RCT)	-	The mean patient-reported discomfort was 43.25	-	MD 23.12 lower (38.36 lower to 7.88 lower)	□□◯◯ Low[c]	One study also shows that the 8/16 patients reported discomfort in NPPV group and 1/12 in HVNI group
Time to successful liberation from assisted ventilation: no. of participants: 0 (0 RCTs)	No primary study reported this outcome					
Hospital length of stay: no. of participants: 120 (3 RCTs)	-	The mean length of stay was 11.5days	-	MD 1.17 days lower (2.38 lower to 0.03 higher)	□◯◯◯ Very low[a,b]	
ICU length of stay: no. of participants: 94 (2 RCTs)		The mean length of stay was 8.0 days		MD 0.95 days lower (6.04 lower to 4.15 higher)	□◯◯◯ Very low[a,b]	
Health-related quality of life: no. of participants: 0 (0 RCTs)	No study reported this outcome					
Failure to oxygenate: no. of participants: 48 (1 RCT)	RR 3.00 (95% CI 0.13–70.17)	0.00%	4.20%	4.2% more (3.8 fewer to 12.2 more)	□□◯◯ Low[c]	
Failure to ventilate: no. of participants: 48 (1 RCT)	RR 0.25 (95% CI 0.03–2.08)	16.70%	4.20%	12.5% fewer (16.2 fewer to 18.0 more)	□□◯◯ Low[c]	
All adverse events: no. of participants: 190 (4 RCTs)	No pooled effect estimate was calculated because adverse-event definitions and reporting differed substantially across trials. Adverse events were therefore summarized descriptively.					

TABLE 3: Summary of findings

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; MD, mean difference; OR, odds ratio; RR, risk ratio

GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level for risk of bias because one contributing trial was judged to be at high risk of bias and methodological concerns remained for some outcome estimates.

b. Downgraded two levels for very serious imprecision because the total sample size and number of events were small and the 95% CI included clinically important benefit and harm.

c. Downgraded for imprecision because the estimate was based on a single small trial with few events.

Search strategy

A systematic search of MEDLINE via PubMed, CENTRAL, EMBASE via Dialog, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov was conducted on August 24, 2025, and updated on October 17, 2026 using the same search strategies. The complete search strategies are presented in Table *4*. We also screened the reference lists of eligible studies and articles citing those studies.

Database or registry	Search strategy	Search date
Cochrane Central Register of Controlled Trials (CENTRAL)	("high velocity therapy":ti,ab OR "high velocity nasal cannula":ti,ab OR Insufflation*:ti,ab OR hvni:ti,ab OR Vapotherm:ti,ab OR "Precision Flow":ti,ab OR HVT:ti,ab OR ProSoft:ti,ab) AND ([mh "Respiratory Insufficiency"] OR "Respiratory Failure":ti,ab OR "Acute respiratory failure":ti,ab OR [mh hypercapnia] OR hypercapnia:ti,ab OR hypercapnic:ti,ab)	August 24, 2025, October 17, 2026
MEDLINE via PubMed	("high velocity therapy"[tiab] OR "high velocity nasal cannula"[tiab] OR "Insufflation*"[tiab] OR hvni[tiab] OR Vapotherm[tiab] OR "Precision Flow"[tiab] OR "HVT"[tiab] OR ProSoft[tiab]) AND ("Respiratory Insufficiency"[Mesh] OR "Respiratory Failure"[tiab] OR "Acute respiratory failure"[tiab] OR hypercapnia[Mesh] OR hypercapnia[tiab] OR hypercapnic[tiab])	August 24, 2025, October 17, 2026
EMBASE	('high velocity therapy':ti,ab OR 'high velocity nasal cannula':ti,ab OR Insufflation*:ti,ab OR hvni:ti,ab OR Vapotherm:ti,ab OR 'Precision Flow':ti,ab OR HVT:ti,ab OR ProSoft:ti,ab) AND ('respiratory failure '/exp OR 'Respiratory Failure':ti,ab OR 'Acute respiratory failure':ti,ab OR hypercapnia/exp OR hypercapnia:ti,ab OR hypercapnic:ti,ab)	August 24, 2025, October 17, 2026
WHO International Clinical Trials Registry Platform (ICTRP)	("high velocity therapy" OR "high velocity nasal cannula" OR "Insufflation*" OR hvni OR Vapotherm OR "Precision Flow" OR "HVT" OR ProSoft) AND ("Respiratory Insufficiency" OR "Respiratory Failure" OR "Acute respiratory failure" OR hypercapnia OR hypercapnic)	August 24, 2025, October 17, 2026
ClinicalTrials.gov	("Respiratory Insufficiency" OR "Respiratory Failure" OR "Acute respiratory failure" OR hypercapnia OR hypercapnia OR hypercapnic) AND ("high velocity therapy" OR "high velocity nasal cannula" OR "Insufflation" OR hvni OR Vapotherm OR "Precision Flow" OR "HVT" OR ProSoft)	August 24, 2025, October 17, 2026

TABLE 4: Search strategy

Data collection and analysis

Selection of the Studies

Two reviewers (CC and JG) separately evaluated records at both the title/abstract and full-text stages. They resolved differing eligibility judgments by discussion with a third reviewer (SK). When essential information was missing, we contacted corresponding authors.

Data Extraction and Management

Using a pilot-tested collection form, two reviewers (CC and JG) separately recorded trial design, participant characteristics, details of the respiratory-support interventions, and prespecified outcome data. A third reviewer (SK)adjudicated unresolved differences between the extracted datasets when necessary.

Assessment of Risk of Bias in Included Studies

Two reviewers (CC and JG) applied the Cochrane Risk of Bias 2 (RoB) tool independently to each eligible trial [19]. They reconciled differing domain-level judgments through discussion, with a third author (SK) adjudicating unresolved assessments.

Measures of Treatment Effects

Treatment effects for dichotomous endpoints were expressed as risk ratios (RRs) with 95% CIs. Continuous endpoints were summarized as mean differences (MDs), or as standardized mean differences when studies used non-equivalent measurement scales. Adverse events were summarized descriptively. When the standard deviation of the mean difference was not provided, we derived it from the reported 95% CI, t-statistic, or p-value.

For length-of-stay outcomes reported as medians and interquartile ranges (IQRs), we estimated the sample mean using the method described by Luo et al. and the standard deviation using the method described by Wan et al. [20,21]. These conversions were applied to the hospital length-of-stay data reported by Abd El Aziz et al. and Elhofy et al. and to the ICU length-of-stay data reported by Elhofy et al. No conversion was performed when the mean and standard deviation were reported directly.

For dichotomous outcomes reported by a single study, study-specific effect estimates with 95% CIs were presented rather than pooled estimates. When one treatment arm contained zero events, a continuity correction of 0.5 was used to calculate the study-specific RR. Because relative effects are difficult to interpret when the comparator arm has zero events, raw event counts, observed absolute risks, and the risk difference were also reported.

Handling of Missing Data

We contacted corresponding authors when information necessary for eligibility assessment or outcome extraction was not available in the published report. Yamane et al. [9] provided additional 14-day data on the composite of intubation or death, and Doshi et al. [22] clarified that identification of the hypercapnic subgroup occurred after randomization. No additional information was obtained because no other responses were received. Missing continuous outcomes were not imputed, following Cochrane guidance [23]. For dichotomous outcomes, denominators were based on the randomized or analyzed population reported by the original study unless otherwise specified.

Assessment of Heterogeneity

We examined between-trial heterogeneity from the forest plots, I^2 values, and Cochran Q statistics. We considered I^2 values above 50% to indicate substantial heterogeneity and used $p<0.10$ for the Q test.

Assessment of Reporting Bias

We compared outcomes specified in trial registrations or protocols with those reported in the corresponding publications to assess selective outcome reporting. Because fewer than 10 studies contributed to every quantitative synthesis, funnel plots and formal statistical tests for funnel-plot asymmetry were not performed.

Meta-analysis

Meta-analyses were performed using the meta package in R software (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria). Dichotomous outcomes were pooled as RRs using the Mantel-Haenszel method, whereas continuous outcomes reported in the same units were pooled as MDs using inverse-variance methods. Random-effects models were used because clinical and methodological heterogeneity across studies was anticipated.

For each outcome, studies were quantitatively synthesized when they evaluated the same intervention-comparator contrast (HVNI versus NPPV) in adults with acute hypercapnic or type II respiratory failure and reported outcomes representing the same clinical construct. Differences in care setting (emergency department, ICU, or general ward) were not considered, by themselves, sufficient grounds to preclude pooling because the underlying clinical comparison was the same. Differences in care setting, underlying etiology, outcome definitions, and follow-up windows were instead considered potential sources of clinical heterogeneity, which motivated use of random-effects models and cautious interpretation of pooled estimates. Study-specific outcome definitions and follow-up periods are reported in Table *2*.

Between-study variance (τ^2) was estimated using the DerSimonian-Laird estimator, and 95% CIs for pooled random-effects estimates were calculated using the Hartung-Knapp adjustment to better account for uncertainty arising from the small number of included studies [24]. Statistical heterogeneity was summarized using τ^2, I^2, and Cochran's Q statistic. For syntheses including at least three studies, 95% prediction intervals were calculated using the Hartung-Knapp method [25]. Prediction intervals were not emphasized for syntheses containing only two studies because between-study heterogeneity could not be estimated reliably with such sparse evidence.

Meta-analysis was not performed when an outcome was reported by only one study; instead, the study-specific effect estimate and its 95% CI were reported. A sensitivity analysis of treatment failure was performed after excluding the trial judged to have the greatest methodological concerns to evaluate the robustness of the pooled estimate to study-level risk of bias.

Trial sequential analysis (TSA) of treatment failure was conducted as a post hoc exploratory analysis to assess the risk of random error arising from sparse cumulative evidence using the RTSA package (version 0.2.2) in R [26]. The analysis assumed a control event proportion of 20%, a relative risk reduction of 20%, a two-sided type I error of 5%, and a type II error of 20% (80% power). A random-effects model with DerSimonian-Laird estimation and Hartung-Knapp adjustment was used with Mantel-Haenszel weighting. The required information size was adjusted for diversity (D^2), and trial sequential monitoring boundaries for efficacy were constructed using an O'Brien-Fleming-type alpha-spending function. No futility boundary was specified.

Summary of Findings Table

Two reviewers (CC and JG) independently rated the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [27]. A third reviewer (SK) resolved any ratings that remained discordant after discussion. The Summary of Findings table was made for the following outcomes, based on the Cochrane handbook [23]: treatment failure, patient-reported discomfort, time to successful liberation from assisted ventilation, hospital length of stay, ICU length of stay, health-related quality of life, failure to oxygenate, failure to ventilate, and adverse events.

Differences between protocol and review

Treatment-Failure Definition

The protocol prespecified treatment failure as the first occurrence of all-cause mortality or unplanned endotracheal intubation. During data extraction, we found that this exact composite could not be reconstructed consistently across all included trials because several studies reported treatment failure using broader study-specific criteria, including crossover, intolerance, inadequate oxygenation or ventilation, and clinical deterioration. We therefore used the study-defined treatment-failure outcome for the primary quantitative synthesis and documented the definition used by each trial in Table *2*. For the study by Shaaban et al., in which a composite treatment-failure outcome was not explicitly reported, treatment failure was derived from the reported intubation and mortality outcomes [10]. This modification was made post hoc and was considered when interpreting the pooled estimate.

Patient-Reported Discomfort

The protocol specified extraction of patient-reported comfort at the time point closest to 72 hours after treatment initiation. However, the only included trial reporting continuous patient-reported comfort data assessed comfort and tolerance at four hours and did not report a later assessment. We therefore used the available four-hour measurement. This change was made after protocol registration and is reported as a protocol deviation.

Outcome Terminology

The protocol specified “duration of mechanical ventilation” as an outcome, defined as the time from randomization to the first episode of at least 48 hours of unassisted breathing or death. In the review, this outcome was renamed “time to successful liberation from assisted ventilation” to better reflect the comparison of HVNI and NPPV. The underlying definition was not modified.

Eligibility Criteria

The protocol defined eligible participants as adults with hypercapnic respiratory failure based on a $PaCO_2$ ⩾60 mmHg or a venous pH of 7.0-7.35. During the review, we recognized that venous pH alone does not establish hypercapnia and that the included trials used different diagnostic thresholds for acute hypercapnic respiratory failure. We therefore clarified the eligibility criterion to include adults with acute hypercapnic or type II respiratory failure as defined by the investigators of the original study, without imposing a uniform $PaCO_2$ or pH threshold across studies. For studies enrolling mixed respiratory-failure populations, separately reported hypercapnic subgroups were considered eligible only when subgroup membership was determined using baseline or pretreatment characteristics assessed before treatment allocation. Post-randomization subgroups defined using information obtained after treatment allocation were excluded because such selection could compromise the randomized comparison. This clarification did not change the set of studies included in the review.

Data Preparation and Statistical Analysis

The protocol specified use of RevMan 5.4.2 with a random-effects model but did not prespecify the Hartung-Knapp adjustment or conversion of medians and IQRs to means and standard deviations. Following peer review and because only a small number of studies contributed to each synthesis, the meta-analyses were repeated in R using DerSimonian-Laird estimation of between-study variance with Hartung-Knapp-adjusted CIs. Hartung-Knapp prediction intervals were additionally calculated for syntheses with at least three studies.

For length-of-stay outcomes reported only as medians and IQRs, means and standard deviations were estimated using the methods of Luo et al. and Wan et al., respectively [20,21]. These data-preparation procedures had not been explicitly prespecified in the protocol.

The protocol anticipated use of SMDs if different validated comfort scales were reported across studies. Because only one study reported continuous discomfort scores, using a visual analog scale, no meta-analysis was possible for this outcome and the study-specific MD with its 95% CI was reported instead.

The protocol proposed visual inspection of funnel plots and formal testing for funnel-plot asymmetry when sufficient studies were available. Because every synthesis contained fewer than 10 studies, and funnel plots would therefore provide little meaningful information, neither funnel plots nor formal tests for asymmetry were performed in the final review.

Subgroup, Sensitivity, and Post Hoc Analyses

The protocol planned subgroup analyses among participants with severe COPD exacerbations, defined by a baseline arterial pH <7.30. These analyses could not be performed because the included studies did not provide sufficient stratified data.

The protocol also planned sensitivity analyses excluding studies in which summary statistics had been imputed. For the length-of-stay outcomes, exclusion of studies requiring conversion of medians and IQRs would have left only one directly reported study for each relevant synthesis, precluding a pooled sensitivity analysis. A sensitivity analysis excluding the study with the greatest methodological concerns was additionally performed for treatment failure; this analysis was not prespecified and was therefore considered post hoc.

Trial sequential analysis was not prespecified in the protocol and was performed as a post hoc exploratory analysis to assess the risk of random error arising from sparse cumulative evidence.

Results

Study Selection

Searches of databases and trial registries yielded 1,433 records. After removal of 443 duplicate records, 990 records underwent title and abstract screening, of which 32 reports were assessed in full text. The updated search conducted on October 17, 2026 identified 96 additional records. After removal of 24 duplicates, 72 unique records were screened and two reports underwent full-text assessment. One of these reports corresponded to a record already identified in the previous search, whereas the other represented one additional eligible randomized controlled trial. Accordingly, four randomized controlled trials were included in the final review [7-10]. We additionally screened 320 records from guidelines [28,29] and 104 records identified through citation searching from the included studies [7-10]. Two potentially relevant reports underwent full-text assessment, both of which corresponded to studies already identified through the database searches [7,8]. The PRISMA flow diagram summarizing the study selection process is presented in Figure *1*. The studies excluded during full-text screening, along with the reasons for exclusion, are listed in Appendix 2.

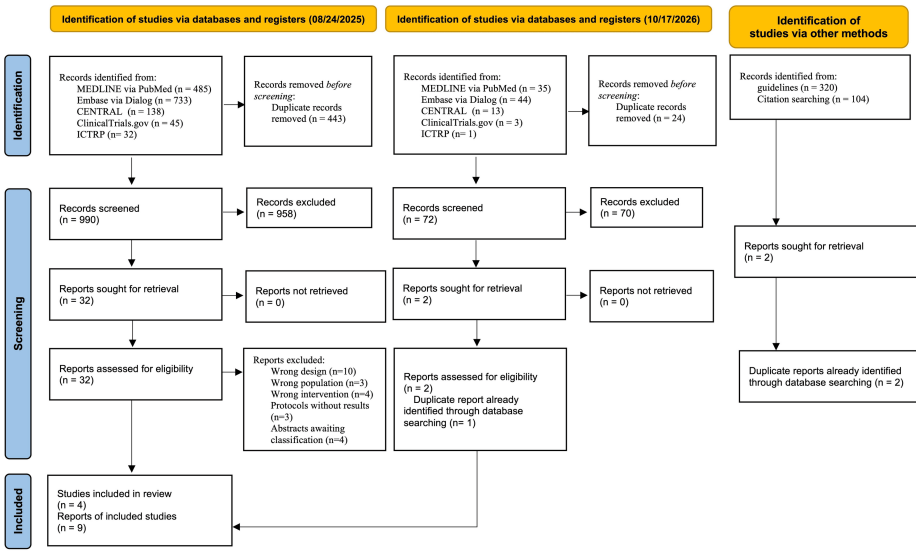


FIGURE 1: PRISMA flowchart of study selection

The diagram summarizes the identification, screening, eligibility assessment, and inclusion of records and randomized controlled trials.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Study Characteristics

The four included RCTs contributed 190 participants to this review, with study sample sizes ranging from 28 to 68 participants. All trials directly compared HVNI with NPPV. The characteristics of each study, including setting, patient population, intervention details, and comparator modalities, are summarized in Table *2*.

Risk-of-bias judgments were outcome-specific (Figure *2*). For treatment failure, Abd El Aziz et al. [7] was judged to be at high risk of bias because of concerns regarding the randomization process, whereas Elhofy et al. [8], Yamane et al. [9], and Shaaban et al. [10] were judged to be at low risk of bias. For hospital length of stay, Abd El Aziz et al. [7] and Elhofy et al. [8] were judged to be at high risk of bias and Shaaban et al. [10] were judged to be at low risk. For ICU length of stay, the study by Elhofy et al. [8] was judged to have some concerns and that by Shaaban et al. was judged to be at low risk. The patient-reported discomfort outcome from Yamane et al. was judged to have some concerns because of missing outcome data and the subjective, unblinded assessment of discomfort. Failure-to-oxygenate and failure-to-ventilate outcomes reported by Elhofy et al. [8] were judged to be at low risk of bias.



FIGURE 2: Risk of bias assessment using the Cochrane Risk of Bias 2 tool

D1, randomization process; D2, deviations from the intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result. Green indicates low risk of bias, yellow indicates some concerns, and red indicates high risk of bias.

Primary Outcomes

Four RCTs involving 190 participants contributed data to the treatment-failure analysis. Random-effects meta-analysis using the DerSimonian-Laird estimator with Hartung-Knapp adjustment showed no clear difference in treatment failure between HVNI and NPPV (RR 0.85, 95% CI 0.30-2.45). Observed heterogeneity was limited numerically (I^2 = 10.4%, τ^2 = 0.048), although these estimates are imprecise given the small number of included studies. The 95% prediction interval ranged from 0.24 to 3.03, reflecting substantial uncertainty regarding the effect that might be observed in a future comparable trial (Figure *3*). The certainty of evidence was rated as very low.

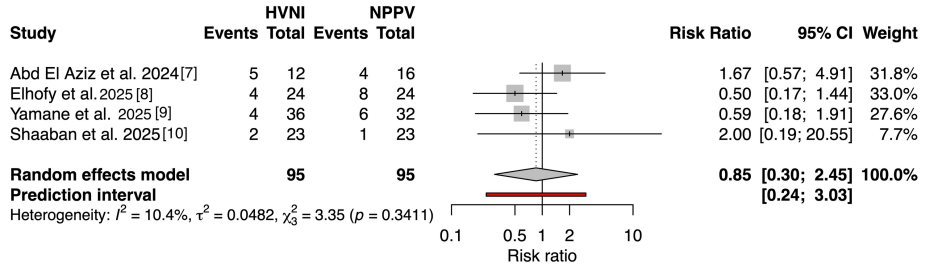


FIGURE 3: Forest plot comparing high-velocity nasal insufflation (HVNI) with noninvasive positive-pressure ventilation (NPPV) for treatment failure

CI, confidence interval; RR, risk ratio.

One RCT reported patient-reported discomfort at four hours. Data were available for 55 of the 68 participants who received the allocated treatment (31 of 36 in the HVNI group and 24 of 32 in the NPPV group), and the analysis was therefore based on available cases. Discomfort was assessed using a 0-100 VAS, with lower scores indicating less discomfort. The study-specific estimate favored HVNI (MD −23.12 points, 95% CI −38.36 to −7.88). However, we did not identify a validated minimal clinically important difference for this specific VAS in patients with acute hypercapnic respiratory failure; therefore, the clinical importance of the magnitude of this difference remains uncertain. The certainty of evidence was rated as low.

No included trial reported time to successful liberation from assisted ventilation according to the prespecified definition. No included trial reported health-related quality of life.

Three RCTs involving 120 participants contributed data for hospital length of stay. Random-effects meta-analysis using the DerSimonian-Laird estimator with Hartung-Knapp adjustment showed no clear difference between HVNI and NPPV (MD −1.17 days, 95% CI −2.38 to 0.03; I^2 = 0%, τ^2 = 0) (Figure *4*). The certainty of evidence was rated as very low.

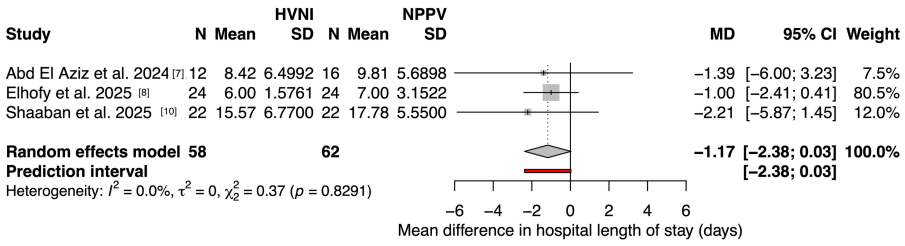


FIGURE 4: Forest plot comparing high-velocity nasal insufflation (HVNI) with noninvasive positive-pressure ventilation (NPPV) for hospital length of stay

CI, confidence interval; MD, mean difference.

Two RCTs involving 94 participants reported ICU length of stay. The pooled estimate favored a shorter ICU stay with HVNI, but the CI was wide and compatible with effects in either direction (MD −0.95 days, 95% CI −6.04 to 4.15; I^2 = 0%, τ^2 = 0) (Figure *5*). The certainty of evidence was rated as very low.

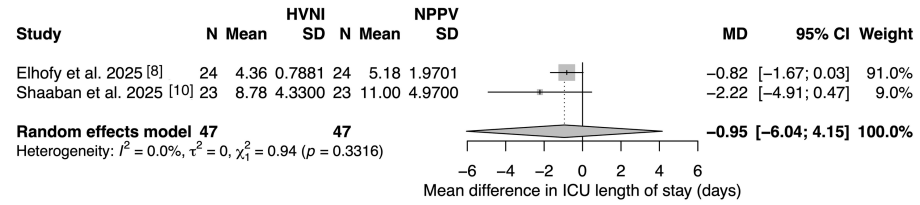


FIGURE 5: Forest plot comparing high-velocity nasal insufflation (HVNI) with noninvasive positive-pressure ventilation (NPPV) for ICU length of stay

CI, confidence interval; ICU, intensive care unit; MD, mean difference.

Secondary Outcomes

Failure to oxygenate was reported by one RCT involving 48 participants [8]. One of 24 participants receiving HVNI (4.2%) and none of 24 participants receiving NPPV (0%) experienced this outcome. Because only one study reported this outcome, no meta-analysis was performed. The study-specific RR, calculated using a continuity correction for the zero-event NPPV arm, was 3.00 (95% CI 0.13-70.17). Given the zero event rate in the comparator group, the observed absolute risk difference was also reported (4.2 percentage points more with HVNI; 95% CI 3.8 percentage points fewer to 12.2 percentage points more). The certainty of evidence was rated as low.

Failure to ventilate was reported by one RCT involving 48 participants. Events occurred in 1 of 24 participants receiving HVNI (4.2%) and 4 of 24 participants receiving NPPV (16.7%). The study-specific RR was 0.25 (95% CI 0.03-2.08), with substantial imprecision. Because only one study contributed data, no meta-analysis was performed. The certainty of evidence was rated as low.

Adverse events and complications were reported inconsistently across the four included trials, and the definitions differed substantially between studies; therefore, no meta-analysis was performed. Interface-related discomfort and nasofacial skin injury were more frequently reported with NPPV in the study by Abd El Aziz et al. [7]. In the study by Shaaban et al., ICU complications were reported in 9 of 23 participants receiving HVNI and 22 of 23 receiving NIV. Facial ulceration occurred in 2 versus 18 participants, agitation in 8 versus 20 participants, and anxiety in 8 versus 20 participants in the HVNI and NIV groups, respectively. Hospital-acquired pneumonia occurred in three participants receiving HVNI and 1 receiving NIV. Given the heterogeneous definitions and incomplete reporting across trials, these findings were summarized descriptively and were not interpreted as establishing comparative safety.

Trial Sequential Analysis

TSA for treatment failure was performed assuming a 20% relative risk reduction, a two-sided α of 5%, and 80% power. The pooled effect estimate was RR 0.85. The cumulative Z-curve did not cross either the conventional significance boundary or the trial sequential efficacy boundary. The diversity-adjusted required information size was 3,246 participants, whereas only 190 participants (5.9%) had been accrued. No futility boundary was specified. Thus, the accrued evidence remained markedly below the required information size and was insufficient to establish a clinically important benefit or harm of HVNI compared with NPPV (Figure *6*).

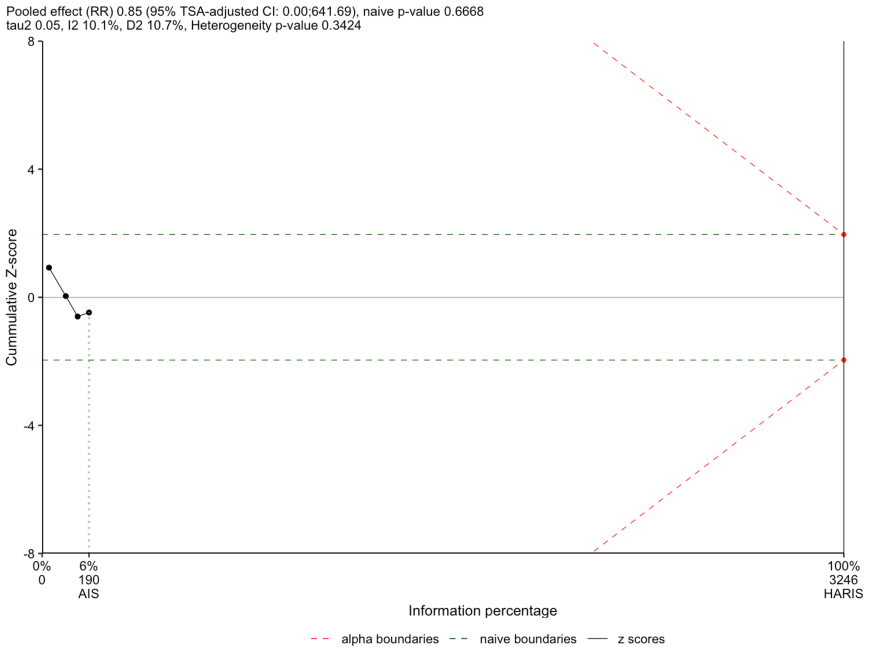


FIGURE 6: Trial sequential analysis for treatment failure

AIS, accrued information size; D², diversity; HARIS, heterogeneity-adjusted required information size; HKSJ, Hartung-Knapp-Sidik-Jonkman; MH, Mantel-Haenszel; RR, risk ratio; RRR, relative risk reduction; TSA, trial sequential analysis.

Reporting Bias

Comparison of registered and published outcomes did not identify major discrepancies in outcome reporting. Funnel plots and formal statistical tests for funnel-plot asymmetry were not performed because fewer than 10 studies contributed to each synthesis, making such assessments uninformative [23].

Subgroup and Sensitivity Analyses

The prespecified subgroup analyses could not be performed because the included studies did not provide sufficient stratified data for participants with severe COPD exacerbations or the other planned subgroups.

A sensitivity analysis of treatment failure excluding Abd El Aziz et al., which had the greatest methodological concerns, included three RCTs with 162 participants. The pooled estimate remained imprecise and did not demonstrate a clear difference between HVNI and NPPV (RR 0.62, 95% CI 0.18-2.11; $I^2 = 0\%$, $\tau^2 = 0$) (Figure 7). Thus, exclusion of this study did not materially alter the interpretation of the primary analysis.

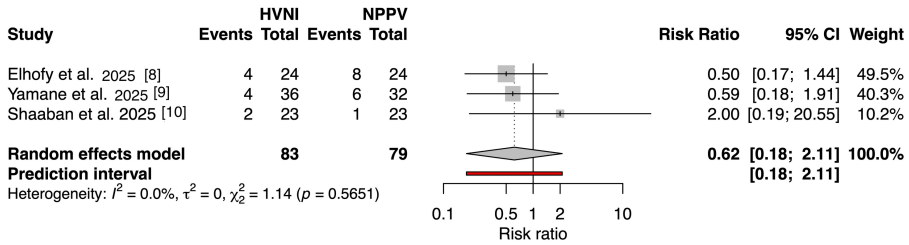


FIGURE 7: Sensitivity analysis for treatment failure after exclusion of the trial judged to have the greatest methodological concerns

CI, confidence interval; RR, risk ratio.

Discussion

Our findings did not demonstrate a clear difference between HVNI and NPPV; however, the evidence was sparse and imprecise and does not establish clinical equivalence. In this systematic review and meta-analysis of four randomized trials including 190 adults with hypercapnic respiratory failure, we did not find a clear difference in treatment failure between HVNI and NPPV. The pooled estimate was imprecise: its CI encompassed clinically relevant effects in either direction. Hospital and ICU length-of-stay estimates were also imprecise, whereas no included trial reported time to successful liberation from assisted ventilation or health-related quality of life. Only one trial reported patient-reported discomfort, with the estimate favoring HVNI; however, the clinical importance of this difference is uncertain because no validated MCID was identified for the scale in this clinical setting. Overall, the certainty of evidence was low to very low, primarily because of substantial imprecision and small sample sizes, with additional concerns regarding risk of bias for some outcomes.

Our findings are broadly consistent with previous systematic reviews evaluating conventional HFNC or high-flow nasal therapy versus NIV in acute hypercapnic respiratory failure. Ovtcharenko et al. found no clear differences in mortality, endotracheal intubation, hospital length of stay, or change in $PaCO_2$ between HFNC and NIV, although the certainty of evidence was generally low [14]. Similarly, Fahey et al. found no significant differences in gas exchange, intubation, mortality, or treatment switching [15]. More recently, Qin et al., focusing specifically on acute exacerbations of COPD with hypercapnic respiratory failure, found no clear differences in mortality or intubation but reported higher treatment-failure and treatment-switch rates with HFNC than with NPPV [16]. These prior reviews primarily evaluated conventional HFNC or broader high-flow nasal therapy and therefore should not be considered directly interchangeable with the HVNI-specific evidence synthesized in the present review.

NPPV remains the guideline-recommended first-line therapy for acute hypercapnic respiratory failure, particularly in acute exacerbations of COPD with acidemia, based on evidence that it reduces the need for intubation and improves survival compared with standard oxygen therapy [4]. However, previous reports also acknowledged that NPPV is frequently limited by poor tolerance, air leaks, claustrophobia, and pressure-related skin injury, and that failure or non-compliance with NPPV is common in routine practice [30]. Relevant supportive evidence also comes from the predefined hypercapnic subgroup analysis of the earlier randomized trial by Doshi et al. [22]. However, this analysis was not included in the quantitative synthesis because the hypercapnic subgroup was selected after randomization using discharge diagnoses, rather than being defined from baseline eligibility criteria before treatment allocation. We considered this post-randomization selection to introduce a potential risk of selection bias and therefore treated the study as complementary rather than eligible randomized evidence.

The available evidence does not demonstrate a clear difference in treatment failure between HVNI and NPPV, although the CI remains compatible with clinically important benefit or harm. Importantly, these findings should not be interpreted as supporting replacement of NPPV by HVNI when NPPV is otherwise indicated. Current European Respiratory Society guidance suggests a trial of NIV before HFNC in patients with COPD and acute hypercapnic respiratory failure. HVNI may therefore be considered primarily when mask-based NPPV is not tolerated or cannot be applied effectively, with close monitoring and prompt escalation when respiratory status deteriorates [28]. Further adequately powered randomized trials are needed to determine the comparative effectiveness and safety of HVNI and NPPV.

The findings underscore the need for larger, methodologically rigorous trials to determine whether HVNI provides clinically meaningful benefits in treatment failure, patient-reported outcomes, or other clinically important endpoints. Existing studies are small and often single-center. Methodological concerns remained for some outcomes, including treatment failure and length-of-stay outcomes, and these concerns were considered in the GRADE assessment. Together with the small sample sizes and substantial imprecision, these limitations reduce confidence in the precision and generalizability of the observed effects. Many trials of high-flow nasal therapies in acute hypercapnic respiratory failure also enroll heterogeneous populations with mixed etiologies and varying degrees of acidosis, complicating indirect comparisons and quantitative synthesis [15,16]. Future research should therefore focus on well-defined hypercapnic populations-such as patients with acute COPD exacerbations or obesity hypoventilation. Studies may also incorporate clear inclusion thresholds for pH and $PaCO_2$, standardized NPPV and HVNI protocols, and uniform composite endpoints that combine intubation and mortality. Trials should be adequately powered, ideally multicenter, and should incorporate patient-centered outcomes, including comfort, dyspnea, communication, and health-related quality of life, alongside traditional physiologic and resource outcomes such as gas exchange, length of stay, and need for escalation of respiratory support.

This review has several strengths. The protocol was prospectively registered, the literature search was updated before publication, study selection and data extraction were performed independently by two reviewers, and risk of bias and certainty of evidence were assessed using the RoB 2 and GRADE frameworks, respectively. Several limitations should also be considered. First, the available evidence was sparse, with only four small randomized trials conducted in different clinical settings and populations. Some trials evaluated a single proprietary HVNI device, which may limit generalizability. Second, definitions and follow-up periods for treatment failure and other outcomes were not fully standardized across studies, and

some outcomes were reported by only one trial. Third, some length-of-stay data were reported as medians and interquartile ranges and required conversion to means and standard deviations for quantitative synthesis. At the review level, the small number of included studies precluded meaningful assessment of small-study effects using funnel plots or formal tests for asymmetry. Prespecified subgroup analyses and some sensitivity analyses could not be performed because sufficient stratified or directly reported data were unavailable. In addition, several analytical modifications, including the Hartung-Knapp adjustment and trial sequential analysis, were introduced after protocol registration and are therefore transparently reported as protocol deviations or post hoc analyses. In addition, the prespecified mortality-or-intubation composite could not be reconstructed consistently across all trials, necessitating use of study-defined treatment failure in the primary synthesis.

Conclusions

In conclusion, the available evidence remains insufficient to determine whether HVNI provides clinically comparable outcomes to NPPV. The available trials remain too small and imprecise to determine whether the physiologic effects of HVNI translate into lower intubation or mortality rates or better patient-reported outcomes.

Appendices

Appendix 1

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	05-Jun
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	04-Jun
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7

Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9
Study characteristics	17	Cite each included study and present its characteristics.	9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-Dec
	23b	Discuss any limitations of the evidence included in the review.	11-Dec
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
		Provide registration information for the review, including register name and registration number, or	

Registration and protocol	24a	state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	In DOI form
Competing interests	26	Declare any competing interests of review authors.	In DOI form
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	In DOI form

TABLE 5: PRISMA checklist

Appendix 2

Title	First author	Reason for exclusion
High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial	Doshi, Pratik	Wrong design
The outcome of early use of high-velocity nasal insufflation in acute respiratory failure complicating coronavirus disease 2019	Bakkar, Lamees M	Wrong population
HVNI vs NIPPV in the treatment of acute decompensated heart failure: Subgroup analysis of a multi-center trial in the ED	Haywood, Steven T.	Wrong design
The ventilatory effect of high velocity nasal insufflation compared to non-invasive positive-pressure ventilation in the treatment of hypercapneic respiratory failure: A subgroup analysis	Doshi, Pratik B.	Wrong design
SAEM Annual Meeting Abstracts	Schreyer, Kraftin E.	Wrong design
SAEM Annual Meeting Abstracts	Doshi P	Wrong design
High Flow Therapy for the Treatment of Respiratory Failure in the ED	NCT02236559	Wrong design
HVNI vs Noninvasive Ventilation for Acute Hypercapnic Respiratory Failure	University, Assiut	Protocols without results
High-Velocity Nasal Insufflation Therapy Versus Non-Invasive Ventilation In Management Of Acute Hypercapnic Respiratory Failure In Obesity Hypoventilation Syndrome: A Randomized Controlled Trial	University, Assiut	Protocols without results
A Randomized Controlled Trial of High-Velocity Nasal Insufflation (HVNI) Versus Noninvasive Ventilation (NIV) for Acute Respiratory Failure of Community-Acquired Pneumonia (CAP).	NCT06996834	Abstracts awaiting classification
Resource utilization and costs of high velocity nasal insufflation compared to non-invasive positive pressure ventilation for respiratory failure	Pietzsch, JB	Wrong design
Prospective, Randomized, Controlled, Open-Label Single-Center Trial Comparing High-Velocity Nasal Insufflation (HVNI) Versus Non-Invasive Ventilation (NIV) for Acute Respiratory Failure in Guillain-Barré Syndrome	NCT06996509	Abstracts awaiting classification
Clinical Efficacy in Relief of Dyspnea by HVNI: evaluation of New Device Equivalence	NCT04590014	Wrong intervention
Assessing Clinical Effect of HVNI on Patient Ambulation in Acute Care Scenarios: a Feasibility Study	NCT03885726	Wrong design

HVNI Versus NIV In Management Of Acute Hypercapnic Respiratory Failure In OHS	NCT05805293	Protocols without results
Clinical Efficacy in Relief of Dyspnea by HVNI: evaluation of New Cannulae Designs	NCT04512781	Wrong intervention
Study of High-velocity Nasal Insufflation Versus Non-invasive Positive Pressure Ventilation for Emergency Type 2 Respiratory Failure: a Non-inferiority Randomized Controlled Trial (The SHINE Trial)	NCT07065656	Abstracts awaiting classification
RolE of High Velocity Nasal Insufflation in imrpoVing wEaning Success in Respiratory Failure Patients (REVIVER)	NCT05855213	Wrong population
Clinical Efficacy in Relief of Dyspnea by HVNI: Evaluation of New Device Equivalence	NCT04590014	Wrong intervention
Clinical Efficacy in Relief of Dyspnea by HVNI: Evaluation of New Device Equivalence	NCT04590014	Wrong intervention
Vapotherm High Flow Therapy for the Treatment of Respiratory Failure in the ED: A Randomized Controlled Trial	NCT02236559	Wrong design
High velocity nasal insufflation in hypercapneic respiratory failure: Secondary analysis of randomized clinical trial	Doshi PB	Wrong design
High Flow Nasal Cannula Versus Non-invasive Ventilation in Prevention of Escalation to Invasive Mechanical Ventilation in Patients With Acute Hypoxemic Respiratory Failure	NCT03788304	Wrong population
HVNI vs NIPPV in Type 2 Respiratory Failure	NCT07065656	Abstracts awaiting classification

TABLE 6: Excluded studies

Each row represents an individual report or registry record assessed for eligibility. Multiple records may correspond to the same underlying study.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Shunsuke Kondo, Yuki Kataoka

Acquisition, analysis, or interpretation of data: Shunsuke Kondo, Collin R. Clarke, Joshua J. Garcia, Brent J. Matsuda, Yuki Kataoka

Drafting of the manuscript: Shunsuke Kondo, Yuki Kataoka

Critical review of the manuscript for important intellectual content: Shunsuke Kondo, Collin R. Clarke, Joshua J. Garcia, Brent J. Matsuda, Yuki Kataoka

Supervision: Brent J. Matsuda, Yuki Kataoka

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Davidson AC, Banham S, Elliott M, et al.: BTS/ICS guideline for the ventilatory management of acute

hypercapnic respiratory failure in adults. Thorax. 2016, 71 Suppl 2:ii1-35. 10.1136/thoraxjnl-2015-208209
2. Russotto V, Myatra SN, Laffey JG, et al.: Intubation practices and adverse peri-intubation events in critically ill patients from 29 countries. JAMA. 2021, 325:1164-72. 10.1001/jama.2021.1727
3. Demoule A, Girou E, Richard JC, Taille S, Brochard L: Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med. 2006, 32:1756-65. 10.1007/s00134-006-0324-1
4. Rochwerg B, Brochard L, Elliott MW, et al.: Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017, 50:1602426. 10.1183/13993003.02426-2016
5. Mehta AB, Douglas IS, Walkey AJ: Hospital noninvasive ventilation case volume and outcomes of acute exacerbations of chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2016, 13:1752-9. 10.1513/AnnalsATS.201603-209OC
6. Cammarota G, Simonte R, De Robertis E: Comfort during non-invasive ventilation. Front Med (Lausanne). 2022, 9:874250. 10.3389/fmed.2022.874250
7. Abd El Aziz AA, Abdelaal GA, Gasad HR, Tawadros BB: High velocity nasal insufflation versus non-invasive ventilation in acute respiratory failure: a comparative study. Egypt J Chest Dis Tuberc. 2024, 73:161-8. 10.4103/ecdt.ecdt_26_23
8. Elhofy MM, Baeis AI, Elshabrawy AM, Elbialy SA: High velocity nasal insufflation vs non-invasive positive pressure ventilation in the management of acute hypercapnic respiratory failure. Alex J Med. 2025, 61:80-7. 10.1080/20905068.2024.2431753
9. Yamane DP, Jones CW, Wilkerson RG, et al.: High-velocity nasal insufflation versus noninvasive positive pressure ventilation for moderate acute exacerbation of chronic obstructive pulmonary disease in the emergency department: a randomized clinical trial. Acad Emerg Med. 2025, 32:403-13. 10.1111/acem.15038
10. Shaaban LH, Mohamed AZE-A, Sadek AH, Khaleel WGE: High-velocity nasal insufflation in the management of overlap syndrome: a randomized clinical trial. Egypt J Bronchol. 2025, 19:69.
11. Miyazaki Y, Inoue S, Hirose H, Kooguchi K, Kotani J: High-velocity nasal insufflation increases nasopharyngeal pressure with flow-dependent manner compared with high flow nasal cannula in adult volunteers - a single-center prospective observational study. Kobe J Méd Sci. 2021, 67:92-7. 10.24546/81013030
12. Möller W, Celik G, Feng S, et al.: Nasal high flow clears anatomical dead space in upper airway models . J Appl Physiol (1985). 2015, 118:1525-32. 10.1152/japplphysiol.00934.2014
13. D'Cruz RF, Hart N, Kaltsakas G: High-flow therapy: physiological effects and clinical applications . Breathe (Sheff). 2020, 16:200224. 10.1183/20734735.0224-2020
14. Ovtcharenko N, Ho E, Alhazzani W, et al.: High-flow nasal cannula versus non-invasive ventilation for acute hypercapnic respiratory failure in adults: a systematic review and meta-analysis of randomized trials. Crit Care. 2022, 26:348. 10.1186/s13054-022-04218-3
15. Fahey AC, O'Connell M, Cornally N, Saab MM: High flow nasal cannula versus noninvasive ventilation in the treatment of acute hypercapnic respiratory failure: a systematic review and meta-analysis. Clin Respir J. 2023, 17:1091-102. 10.1111/crj.13695
16. Qin J, Wang G, Liao Y, Shang W, Han D: High flow nasal therapy versus noninvasive ventilation for AECOPD with acute hypercapnic respiratory failure: a meta-analysis of randomized controlled trials. Ann Intensive Care. 2025, 15:64. 10.1186/s13613-025-01480-w
17. Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021, 372:n71. 10.1136/bmj.n71
18. Efficacy of high-velocity nasal insufficiation in the treatment for respiratory failure: systematic review and meta-analysis, protocol. (2026). Accessed: June 23, 2026: https://osf.io/by3je/overview.
19. Sterne JA, Savović J, Page MJ, et al.: RoB 2: a revised tool for assessing risk of bias in randomised trials . BMJ. 2019, 366:l4898. 10.1136/bmj.l4898
20. Luo D, Wan X, Liu J, Tong T: Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018, 27:1785-805. 10.1177/0962280216669183
21. Wan X, Wang W, Liu J, Tong T: Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014, 14:135. 10.1186/1471-2288-14-135
22. Doshi PB, Whittle JS, Dungan G, et al.: The ventilatory effect of high velocity nasal insufflation compared to non-invasive positive-pressure ventilation in the treatment of hypercapneic respiratory failure: a subgroup analysis. Heart Lung. 2020, 49:610-5. 10.1016/j.hrtlng.2020.03.008
23. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4 . (2023). Accessed: May 31, 2026: https://www.cochrane.org/authors/handbooks-and-manuals/handbook#previous-versions.
24. IntHout J, Ioannidis JP, Borm GF: The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014, 14:25. 10.1186/1471-2288-14-25
25. Riley RD, Higgins JP, Deeks JJ: Interpretation of random effects meta-analyses . BMJ. 2011, 342:d549. 10.1136/bmj.d549
26. Wetterslev J, Jakobsen JC, Gluud C: Trial sequential analysis in systematic reviews with meta-analysis . BMC Med Res Methodol. 2017, 17:39. 10.1186/s12874-017-0315-7
27. Guyatt G, Oxman AD, Akl EA, et al.: GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011, 64:383-94. 10.1016/j.jclinepi.2010.04.026
28. Oczkowski S, Ergan B, Bos L, et al.: ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. Eur Respir J. 2022, 59: 10.1183/13993003.01574-2021
29. Goel NN, Ferreyro BL, Pitre T, et al.: Noninvasive respiratory support for adult patients with acute respiratory failure: an official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2026, 212:2135-58. 10.1093/ajrccm/aamag302
30. Scala R, Pisani L: Noninvasive ventilation in acute respiratory failure: which recipe for success? . Eur Respir Rev. 2018, 27:180029. 10.1183/16000617.0029-2018