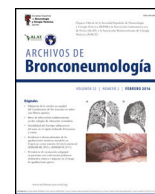




ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Original Article

High-flow Nasal Therapy vs Noninvasive Ventilation for Post-extubation Patients at High Risk of Reintubation: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Jinlv Qin^{a,1}, Yixing Liao^{b,1}, Xu Liao^{c,1}, Guizuo Wang^d, Dong Han^{d,*}

^a Radioimmunoassay Center, Shaanxi Provincial People's Hospital, No. 256, West Youyi Road, Xi'an, Shaanxi 710068, China

^b Department of Critical Care Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310003, China

^c Neurocritical Rehabilitation Unit, Care Alliance Jinchun Rehabilitation Hospital of Chengdu, Chengdu, Sichuan 610066, China

^d Department of Respiratory and Critical Care Medicine, Shaanxi Provincial People's Hospital, No. 256, West Youyi Road, Xi'an, Shaanxi 710068, China

ARTICLE INFO

Article history:

Received 7 December 2025

Accepted 3 April 2026

Available online xxx

Keywords:

HFNC

NIV

Post-extubation

Reintubation

Mortality

ABSTRACT

Background: Current guidelines recommend noninvasive ventilation (NIV) over high-flow nasal cannula (HFNC) in patients at high risk of extubation failure. This systematic review and meta-analysis aimed to compare the efficacy of HFNC vs NIV in post-extubation patients at high risk of reintubation.

Methods: A systematic search was conducted in PubMed, Embase, Cochrane Library, and ClinicalTrials.gov without language restrictions. Randomized controlled trials (RCTs) evaluating HFNC vs NIV in post-extubation patients were included. The primary outcome was reintubation within 72 h. Effect estimates were pooled as risk ratios (RR) with 95%CI. Certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework and categorized as high, moderate, low, or very low.

Results: Eleven RCTs ($n = 2765$ patients) met inclusion criteria. No statistically significant differences were observed between HFNC and NIV for reintubation within 72 h (RR, 1.22; 95%CI, 0.83–1.80; moderate), reintubation within 7 days (RR, 1.23; 95%CI, 0.90–1.69; low), post-extubation respiratory failure (RR, 0.82; 95%CI, 0.66–1.02; moderate), intensive care unit (ICU) mortality (RR, 0.90; 95%CI, 0.63–1.29; very low), in-hospital mortality (RR, 0.96; 95%CI, 0.74–1.25; moderate), or 28-day mortality (RR, 0.99; 95%CI, 0.59–1.65; moderate).

Conclusions: Compared with NIV, HFNC was not associated with increased reintubation or mortality. However, variability in study definitions may limit direct applicability to bedside decision-making in individual high-risk patients.

© 2026 The Author(s). Published by Elsevier España, S.L.U. on behalf of SEPAR. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Noninvasive ventilation (NIV) has been proposed as a strategy to prevent post-extubation respiratory failure and the need for reintubation, particularly in patients at high risk of extubation failure [1].

There is no universally accepted definition of “patients at high risk of extubation failure.” In general, this population includes patients who develop hypercapnia during the spontaneous breathing trial (SBT), those with chronic cardiac or respiratory disease, older adults, and individuals with impaired airway patency [2].

Guidelines from the European Respiratory Society (ERS) and the American Thoracic Society (ATS) recommend NIV over high-flow nasal cannula (HFNC) in patients at high risk of extubation failure, unless contraindications to NIV are present [1,3].

Compared with NIV, HFNC offers improved patient comfort, reduces adverse events related to interface intolerance, and may represent a more tolerable alternative [4]. Its ease of use and better tolerability have led to increasing adoption in post-extubation care [5]. However, its role in patients at high risk of reintubation remains uncertain.

Therefore, the aim of this study was to perform a systematic review and meta-analysis of RCTs to determine whether HFNC is noninferior to NIV in post-extubation patients at high risk of reintubation.

* Corresponding author.

E-mail address: sesory@yeah.net (D. Han).

¹ Contributed equally.

Methods

Data sources and search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6]. The protocol was registered in April 2025 in the PROSPERO database (ID: 1036660; registration pending confirmation).

PubMed, Embase, Cochrane Library, and ClinicalTrials.gov were searched for relevant studies published up to April 27, 2025.

Study selection

Given heterogeneity in definitions and inclusion criteria across studies, which may introduce variability in study populations, we selected the relatively objective outcome of tracheal reintubation rate as the primary inclusion criterion.

Studies were eligible if they met the following criteria: (a) included adult post-extubation patients at high risk of reintubation (defined as a reintubation rate $\geq 10\%$ at 72 h or 7 days in either HFNC or NIV groups); (b) used a randomized controlled design comparing HFNC with NIV (including bilevel positive airway pressure [BiPAP]); and (c) reported outcomes including reintubation or mortality.

The PubMed search strategy included the following terms: (“high flow” OR “HFNC” OR “HFNO” OR “HFNT” OR “HFNP”) AND (“NIV” OR “non-invasive” OR “noninvasive” OR “BiPAP” OR “NIPPV”) AND (“high risk” OR “reintubation” OR “extubation” OR “extubating”).

Reference lists of relevant review articles were also screened to identify additional eligible studies. No language restrictions were applied. Full search strategies for all databases are provided in Table S1.

Data extraction and quality assessment

Two reviewers independently screened articles according to the predefined inclusion criteria. Discrepancies were resolved by consensus. Standardized data extraction forms were used to collect relevant information from the text, tables, and figures of each included trial, including study characteristics (author, year of publication or last update), patient demographics (sample size, age), and baseline clinical variables (body mass index [BMI], arterial pH, arterial carbon dioxide partial pressure [PaCO₂], arterial oxygen partial pressure [PaO₂], and PaO₂/fraction of inspired oxygen [FiO₂]).

Outcomes extracted included reintubation within 72 h, reintubation within 7 days, intensive care unit (ICU) mortality, in-hospital mortality, 28-day mortality, post-extubation respiratory failure, ventilator-associated pneumonia (VAP), and treatment switching (HFNC to NIV or NIV to HFNC).

Risk of bias assessment

Two reviewers independently assessed the risk of bias using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized controlled trials [7]. Five domains were evaluated: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported results.

Endpoints

The primary endpoint was reintubation within 72 h. Secondary endpoints included reintubation within 7 days, post-extubation respiratory failure, treatment switching, ICU mortality, in-hospital

mortality, 28-day mortality, and ventilator-associated pneumonia (VAP).

Data synthesis and statistical analysis

Meta-analyses were performed when appropriate; otherwise, results were summarized narratively. Statistical analyses were conducted using Review Manager (RevMan), version 5.1 (The Cochrane Collaboration).

For dichotomous outcomes, pooled estimates were expressed as risk ratios (RR) with 95%CI. Heterogeneity was assessed using the χ^2 test and the I^2 statistic. A chi-square test with $P \leq .10$ or $I^2 \geq 50\%$ was considered indicative of significant heterogeneity. A random-effects model was applied.

Prespecified subgroup analyses were conducted according to PaCO₂ levels. Statistical significance was defined as $P < .05$. Sensitivity analyses included restriction to trials at low risk of bias and leave-one-out analyses.

Publication bias was assessed using Egger's linear regression test (Stata version 12.0), with $P < .05$ indicating potential bias.

Trial sequential analysis (TSA)

Trial sequential analysis (TSA) was performed using TSA software (version 0.9.5.10) to evaluate the robustness of the evidence with respect to type I and type II errors and to estimate the required information size (RIS), defined as the cumulative sample size needed to detect a statistically significant difference between treatments [8].

Trial sequential monitoring boundaries (TSMBs) were calculated to determine statistical significance adjusted for accrued sample size. Evidence was considered conclusive when the Z-curve crossed the TSMB for benefit or harm before reaching the RIS.

Certainty of evidence

The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [9].

Results

Study selection and characteristics

Of 1901 records identified in the initial search, 37 articles were retrieved for full-text assessment, and 11 RCTs [10–20] met the inclusion criteria (Fig. 1). Baseline characteristics of the included studies are presented in Table 1.

This meta-analysis focused on the preventive use of HFNC and NIV following extubation. Among the 11 included RCTs, 6 were multicenter [10,12–14,17,18] and 5 were single-center [11,15,16,19,20] studies.

The study populations varied: one trial included patients with obesity (BMI ≥ 30) [10]; three included patients with acute exacerbation of COPD (AECOPD) [11,15,18]; two included patients with at least one risk factor for reintubation [12,16]; one included patients with ≥ 4 risk factors [13]; one included patients with BMI >30 and ≤ 3 risk factors [14]; one included patients after cardiothoracic surgery [17]; one included patients with sepsis [19]; and one included patients receiving prolonged mechanical ventilation (≥ 14 days) [20].

All included trials were published within the past 10 years. Sample sizes ranged from 40 to 830 participants. A total of 2765 patients were included, with 1368 assigned to HFNC and 1397 to NIV.

Details of HFNC and NIV settings are summarized in Table S2.

Table 1
Baseline characteristics of trials included in the meta-analysis.

Study (Ref. no.)	Year	Timing of intervention	Device/mode	n	Age, y (SD)	Male, %	BMI, kg/m ² (SD)	PaCO ₂ , mmHg (SD)	PaO ₂ , mmHg (SD)	Arterial pH (SD)	PaO ₂ /FiO ₂ (SD)
De Jong [10]	2023	Within 30 min after extubation	HFNC/BiPAP	246/245	61 (14)/61 (14)	58/63	35.5 (5.3)/35.4 (4.9)	39 (8)/39 (8)	90 (33)/91 (30)	7.42 (0.07)/7.42 (0.07)	246 (98)/255 (95)
Fang [11]	2021	After extubation	HFNC (Fisher & Paykel)/BiPAP (V60, Philips)	20/24	67.9 (6.9)/72.3 (7.8)	70/46	24.5 (3.5)/26.3 (10.5)	39.4 (6.5)/40.0 (8.9)	106.4 (22.2)/109.9 (21.3)	7.40 (0.06)/7.41 (0.07)	NR
Hernández [12]	2016	Immediately after extubation	HFNC (Optiflow, Fisher & Paykel)/BiPAP (Vision, Respironics)	290/314	64.6 (15.4)/64.4 (15.8)	64/64	NR	41 (2.2)/39 (3.2)	NR	7.39 (0.3)/7.40 (0.2)	191 (34)/194 (37)
Hernández [13]	2022	Immediately after extubation	HFNC (Optiflow)/BiPAP (V60/V60 Plus, Philips)	90/92	59.9 (15.4)/60.9 (14.3)	56/73	NR	41.6 (6.9)/44.2 (8.6)	102.7 (34.8)/116.2 (41.1)	7.42 (0.1)/7.39 (0.2)	NR
Hernández [14]	2025	Immediately after extubation	HFNC (Airvo-2)/BiPAP (V60/V60 Plus)	72/72	60 (49-67)*/62 (54-67)*	56/54	33 (32-35)*/33 (32-36)*	40 (38-42)*/39 (35-42)*	104 (89-127)*/103 (86-126)*	7.41 (7.36-7.46)*/7.45 (7.42-7.49)*	NR
Ketan [15]	2023	Immediately after extubation	HFNC/BiPAP	30/32	65.3 (7.8)/65.4 (9.8)	67/69	NR	48 (7.9) 47 (4.8)	70.4 (11.8)/65.7 (11.3)	7.42 (0.04)/7.42 (0.03)	244.7 (72)/267.8 (48)
Kumari [16]	2024	After extubation	HFNC/BiPAP	30/30	53 (16.7)/54 (18.7)	70/67	27.2 (2.7)/28.1 (3.1)	41.7 (6.6)/42.5 (6.6)	NR	7.40 (0.06)/7.40 (0.07)	253 (70)/268 (71)
Stéphan [15]	2015	After extubation	HFNC (Optiflow)/BiPAP (Vision, Evita XL/4, Monnal T75)	414/416	63.8 (NR)/63.9 (NR)	66/67	28.3 (NR)/28.2 (NR)	38.7 (NR)/39.1 (NR)	NR	7.39 (NR)/7.39 (NR)	196 (NR)/203 (NR)
Tan [18]	2020	Immediately after extubation	HFNC (Airvo-2)/BiPAP (V60, Vision)	44/42	68.4 (9.3)/71.4 (7.8)	64/56	NR	51 (48-58)*/53 (49-61)*	NR	7.48 (7.42-7.51)*/7.45 (7.40-7.49)*	239 (47)/229 (42)
Tongyoo [19]	2021	Immediately after extubation	HFNC (Optiflow)/BiPAP (Carina, Dräger)	112/110	62.6 (18.0)/63.0 (17.5)	54/56	NR	34.2 (6.8)/35.3 (6.6)	139.5 (41.2)/138.4 (37.2)	7.45 (0.05)/7.45 (0.06)	351 (101)/348 (89)
Tseng [20]	2023	After extubation	HFNC (Optiflow)/BiPAP (Trilogy 202)	20/20	74 (11)/73 (13)	50/65	NR	39 (8.3)/38 (6.4)	NR	7.50 (0.04)/7.50 (0.05)	316 (139)/373 (150)

BiPAP, bi-level positive airway pressure; BMI, body mass index; FiO₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula; NR, not reported; PaCO₂, arterial carbon dioxide partial pressure; PaO₂, arterial oxygen partial pressure; SD, standard deviation.

* Values are reported as median (IQR).

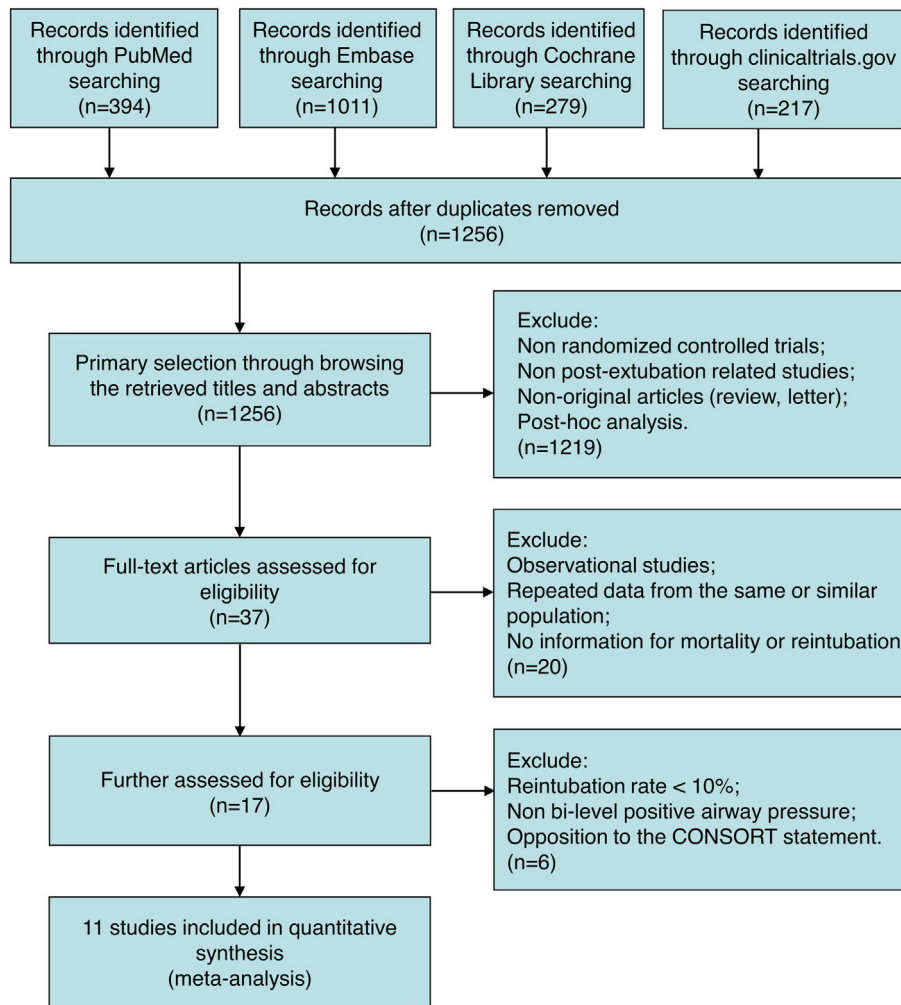


Fig. 1. Study selection flow diagram (PRISMA).

Risk of bias assessments are presented in Fig. S1. Four studies (36.4%) were judged to be at low risk of bias, whereas seven studies (63.6%) raised some concerns. No study was classified as high risk of bias.

Reintubation within 72 h

Data on reintubation within 72 h were extracted from 6 RCTs (1479 patients). There was no statistically significant difference between groups (RR, 1.22; 95%CI, 0.83–1.80; $P=.32$; moderate-certainty evidence [Fig. 2A]), with rates of 18.41% in the HFNC group and 15.31% in the NIV group.

Moderate heterogeneity was observed ($I^2 = 47%$; $P=.09$). Egger's test ($P=.80$) did not indicate publication bias. Trial sequential analysis (TSA) showed that neither conventional thresholds for benefit or harm nor trial sequential monitoring boundaries (TSMBs) for benefit, harm, or futility were reached (Fig. S2). Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate (Table S3).

Reintubation within 7 days

Data from 7 RCTs (1952 patients) were available. There was no statistically significant difference between groups (RR, 1.23; 95%CI, 0.90–1.69; $P=.20$; low-certainty evidence [Fig. 2B]), with rates of 19.32% vs 16.24%.

Moderate heterogeneity was observed ($I^2 = 53%$; $P=.05$). Egger's test ($P=.06$) did not demonstrate significant publication bias. TSA indicated that neither conventional thresholds nor TSMBs were reached (Fig. S3). Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate (Table S3).

Post-extubation respiratory failure

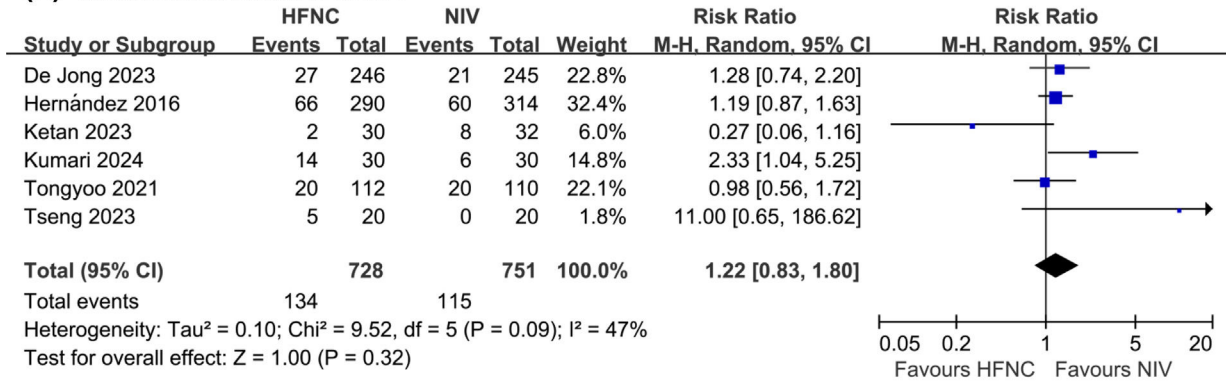
Four RCTs (1420 patients) reported this outcome. Although minor variations existed, definitions were broadly consistent across studies and included respiratory acidosis, severe hypoxemia, increased respiratory rate, decreased level of consciousness, respiratory muscle fatigue, hypotension, and ineffective cough (Table S4).

There was no statistically significant difference between groups (RR, 0.82; 95%CI, 0.66–1.02; $P=.07$; moderate-certainty evidence [Fig. 2C]). The rate was 23.96% in the HFNC group and 30.57% in the NIV group.

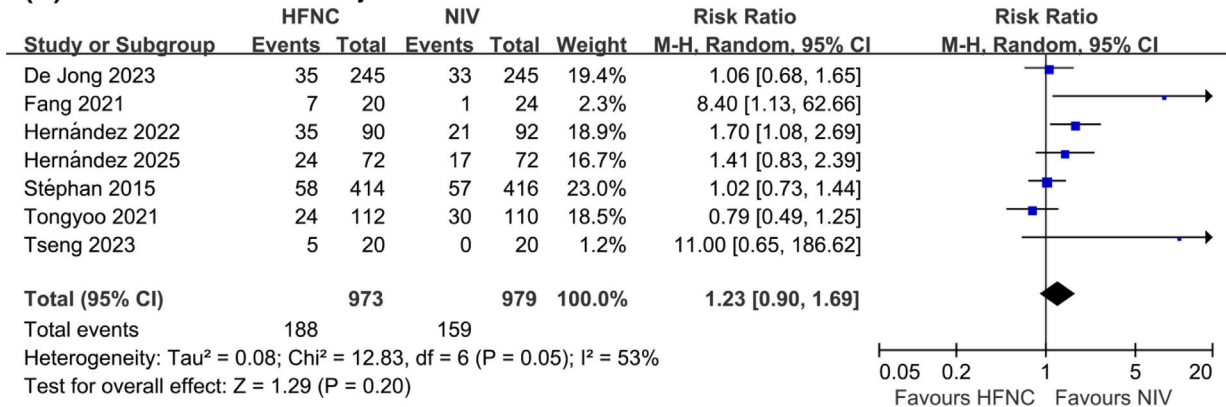
Low heterogeneity was observed ($I^2 = 33%$; $P=.22$). Egger's test ($P=.35$) did not indicate publication bias. TSA showed that no thresholds or TSMBs were reached (Fig. S4).

However, leave-one-out sensitivity analysis indicated instability of the pooled estimate, as statistical significance changed after exclusion of the study by Hernández et al [13] (Table S3).

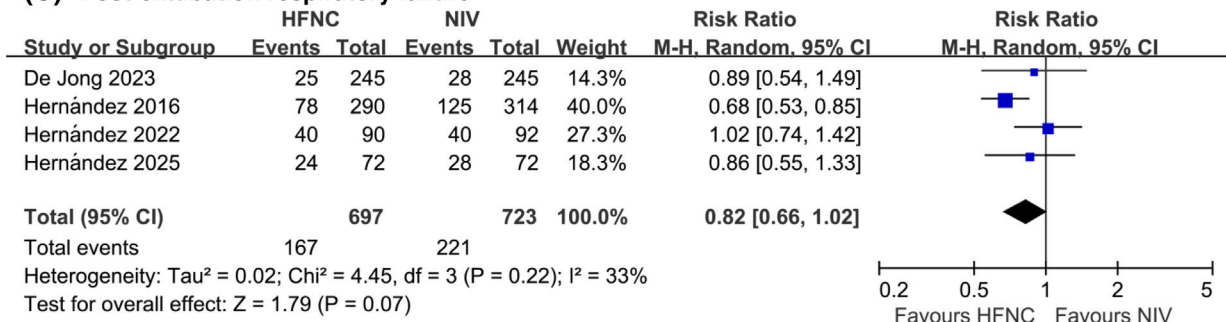
(A) Reintubation within 72 hours



(B) Reintubation within 7 days



(C) Post-extubation respiratory failure



(D) Treatment switch

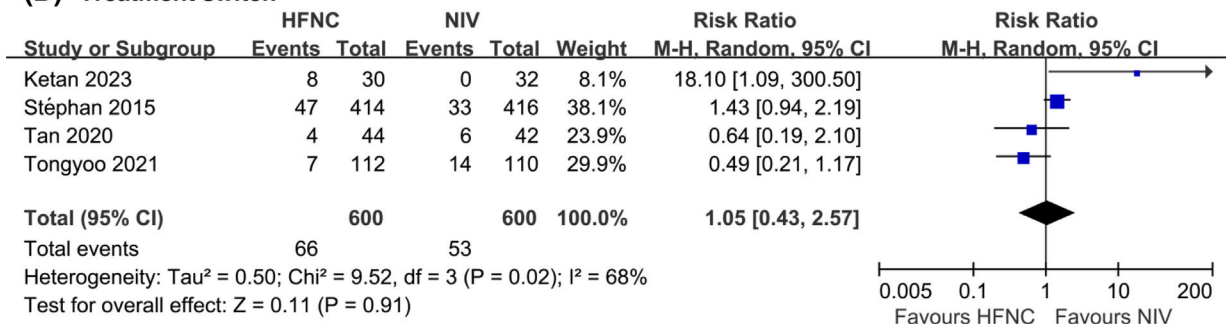


Fig. 2. Forest plots (HFNC vs NIV outcomes). Effect estimates are presented as risk ratios (RR) with 95%CI. (A) Reintubation within 72 h. (B) Reintubation within 7 days. (C) Post-extubation respiratory failure. (D) Treatment switch.

Treatment switch

Four RCTs (1200 patients) reported treatment switching. There was no statistically significant difference between groups (RR, 1.05;

95%CI, 0.43–2.57; P=.91; low-certainty evidence [Fig. 2D]), with rates of 11.00% vs 8.83%.

Substantial heterogeneity was observed (I² = 68%; P=.02). Egger’s test (P=.996) did not indicate publication bias. TSA showed

that no thresholds or TSMBs were reached (Fig. S5). Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate (Table S3).

ICU mortality

Six RCTs (2471 patients) reported ICU mortality. There was no statistically significant difference between groups (RR, 0.90; 95%CI, 0.63–1.29; $P = .56$; very low-certainty evidence [Fig. 3A]). Mortality rates were 6.54% in the HFNC group and 7.05% in the NIV group.

Low heterogeneity was observed ($I^2 = 27%$; $P = .23$). Egger's test ($P = .007$) suggested the presence of publication bias. TSA indicated that no thresholds or TSMBs were reached (Fig. S6). Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate (Table S3).

In-hospital mortality

Five RCTs (1196 patients) reported in-hospital mortality. There was no statistically significant difference between groups (RR, 0.96; 95%CI, 0.74–1.25; $P = .77$; moderate-certainty evidence [Fig. 3B]). Mortality rates were 16.78% vs 17.48%.

No heterogeneity was observed ($I^2 = 4%$; $P = .39$). Egger's test ($P = .32$) did not indicate publication bias. TSA showed that no thresholds or TSMBs were reached (Fig. S7). Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate (Table S3).

28-Day mortality

Data on 28-day mortality were extracted from 3 RCTs (797 patients). There was no statistically significant difference between groups (RR, 0.99; 95%CI, 0.59–1.65; $P = .96$; moderate-certainty evidence [Fig. 3C]).

No heterogeneity was observed ($I^2 = 0%$; $P = .76$). The 28-day mortality was 6.73% in the HFNC group and 6.82% in the NIV group. Egger's test ($P = .64$) did not indicate publication bias. TSA showed that neither conventional thresholds for benefit or harm nor trial sequential monitoring boundaries (TSMBs) for benefit, harm, or futility were reached (Fig. S8). Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate (Table S3).

Ventilator-associated pneumonia

Three RCTs (930 patients) reported ventilator-associated pneumonia (VAP) occurring after reintubation. In the included studies, VAP was defined consistently as fever (temperature $>38^\circ\text{C}$) or abnormal leukocyte count ($>12,000/\text{mL}$ or $<4000/\text{mL}$), plus new purulent endotracheal secretions or change in sputum, in combination with new, progressive, or persistent infiltrate, consolidation, or cavitation, and significant pathogen culture ($>10^5$ cfu/mL in semi-quantitative endotracheal aspirate, $>10^4$ cfu/mL in bronchoalveolar lavage fluid, or $>10^3$ cfu/mL in protected brush specimens).²¹

There was no statistically significant difference between groups (RR, 0.97; 95%CI, 0.56–1.68; $P = .91$; moderate-certainty evidence [Fig. 3D]), with rates of 5.31% vs 5.44%.

No heterogeneity was observed ($I^2 = 0%$; $P = .49$). Egger's test ($P = .38$) did not indicate publication bias. TSA showed that no thresholds or TSMBs were reached (Fig. S9). Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate (Table S3).

Certainty of evidence

The GRADE assessment is summarized in Table S5. Certainty of evidence was rated as moderate for reintubation within 72 h,

post-extubation respiratory failure, 28-day mortality, in-hospital mortality, and ventilator-associated pneumonia; low for reintubation within 7 days and treatment switch; and very low for ICU mortality.

The most common reason for downgrading was inconsistency across studies.

Subgroup analysis

Given that NIV may be more effective in patients with hypercapnia, subgroup analyses stratified by baseline PaCO₂ (>45 mmHg vs ≤ 45 mmHg) were performed. Results are presented in Table S6.

Restriction to low-risk-of-bias trials

To address heterogeneity, analyses restricted to trials at low risk of bias were conducted. Results are summarized in Table S7.

Discussion

The aim of this meta-analysis was to compare the efficacy of HFNC and NIV in post-extubation patients at high risk of reintubation. Based on current evidence, no statistically significant differences were observed between groups in terms of reintubation or mortality outcomes.

However, several pooled estimates were imprecise, with wide confidence intervals compatible with both clinically meaningful benefit and harm. These findings likely reflect limited statistical power and between-study heterogeneity rather than true equivalence between treatments. Moreover, variability in mortality endpoints across trials and the overall low incidence of events further limit interpretability. Therefore, the absence of statistically significant differences should not be interpreted as evidence of no clinically relevant effect.

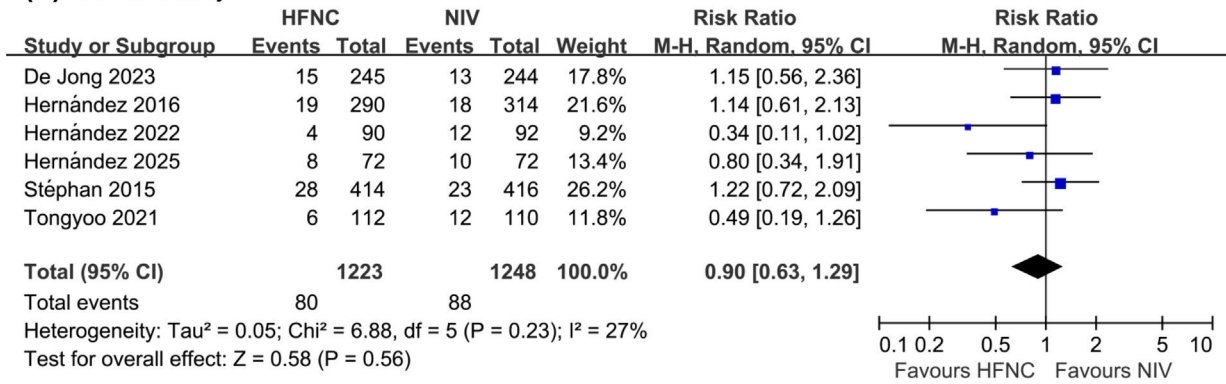
Leave-one-out sensitivity analysis identified the study by Hernández et al. [13] as influential, as its exclusion altered the pooled estimate for post-extubation respiratory failure. This study included patients with a higher burden of risk factors (≥ 4) and reported the highest reintubation rate among included trials, which may explain its disproportionate impact.

Notably, a post hoc analysis of the Hernández et al., 2016 study [22] suggested that patients with ≥ 4 risk factors for reintubation may derive greater benefit from prophylactic NIV. This finding highlights the potential importance of patient selection and risk stratification when comparing HFNC and NIV in clinical practice.

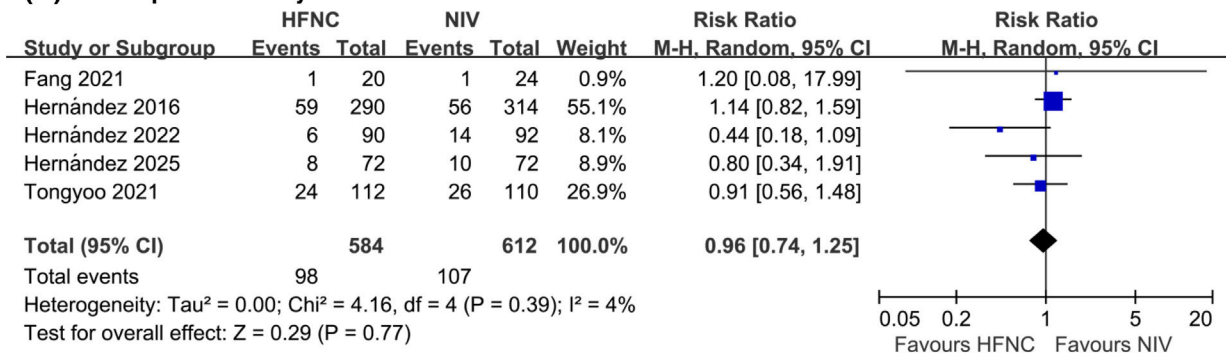
Weaning is defined as the gradual reduction of ventilatory support in patients whose underlying cause of respiratory failure is improving [23]. In most studies, weaning failure is defined as the inability to successfully complete a spontaneous breathing trial (SBT) or the need for reintubation within 48 h after extubation [24]. However, more recent studies [25] have adopted a more conservative definition of weaning success – namely, the absence of reintubation within 7 days of extubation – thereby capturing events over a longer post-extubation period. This approach may be more rigorous than earlier definitions using shorter timeframes [26], as it reduces the risk of misclassifying patients who require delayed reintubation as successful weaning cases. Accordingly, in the present meta-analysis, both 72-h and 7-day reintubation windows were used to provide a more comprehensive evaluation of the effects of HFNC and NIV.

Because the use of NIV as rescue therapy for established post-extubation respiratory failure has not been shown to improve outcomes [1], clinical focus has shifted toward prevention of respiratory failure and reintubation. Current European Respiratory Society (ERS) recommendations favor the use of NIV over HFNC in

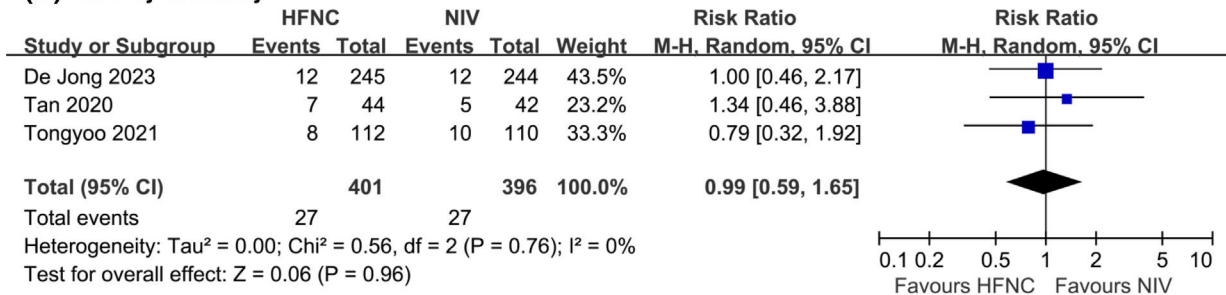
(A) ICU mortality



(B) In-hospital mortality



(C) 28-Day mortality



(D) Ventilator-associated pneumonia

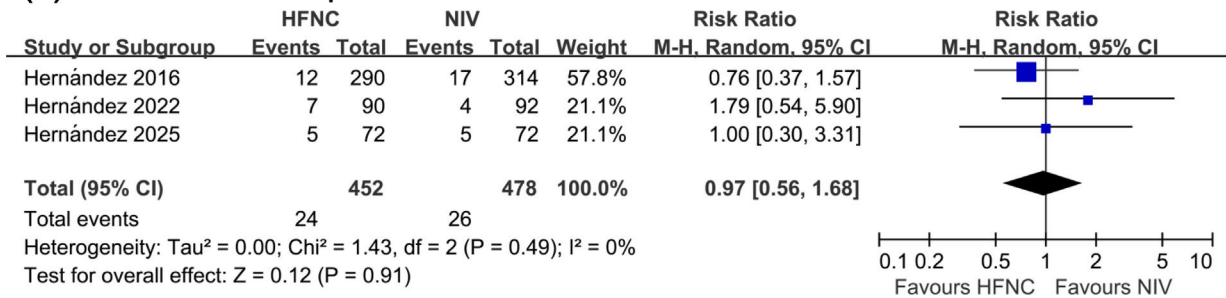


Fig. 3. Forest plots (mortality and VAP outcomes). Effect estimates are presented as risk ratios (RR) with 95%CI. (A) ICU mortality. (B) In-hospital mortality. (C) 28-Day mortality. (D) Ventilator-associated pneumonia.

patients at high risk of extubation failure, unless contraindications are present [1].

Recent expert consensus suggests that post-extubation respiratory support should be individualized according to patient risk profiles. For example, humidified NIV may be preferred in patients at very high risk or in obese patients with intermediate risk of hypoxemic failure. More broadly, NIV-based strategies may be appropriate for high-risk patients, including those with obesity or

hypercapnia at the end of the SBT. Patients at intermediate risk may receive either HFNC or NIV depending on individualized clinical factors, whereas HFNC alone may be sufficient for low-risk patients [27].

Although both HFNC and NIV have demonstrated superiority over conventional oxygen therapy, the optimal noninvasive respiratory support strategy for individual patients remains uncertain [28]. Several predictive models for extubation failure have been

proposed; however, their clinical applicability remains limited [25,29]. Furthermore, the commonly used definition of “high risk” based on the presence of ≥ 1 risk factor may introduce substantial heterogeneity across study populations [29,30].

Certain subgroups of high-risk patients may derive greater benefit from NIV. These include patients identified by Thille et al. [31] (e.g., elderly individuals, obese patients, those receiving prolonged mechanical ventilation ≥ 7 days, patients with ineffective cough, or those with underlying chronic cardiac or pulmonary disease) and those described by Ferrer et al. [32] (patients who develop hypercapnia at the end of the SBT).

Despite these insights, important knowledge gaps remain. First, it is unclear whether specific risk factors confer differential benefit from distinct noninvasive strategies. Second, although prior studies have suggested synergistic interactions among risk factors for reintubation (e.g., advanced age combined with cardiac or respiratory disease, or secretion burden combined with impaired cough and neurological status) [33], the potential additive effects of multiple risk factors – and their influence on treatment response – remain insufficiently characterized [22].

A recent post hoc analysis [34] evaluated the diagnostic accuracy of several predictive models in 2341 patients enrolled in 5 multicenter randomized trials conducted in Spain [12–14,35,36]. Three models were assessed: a 3-factor model (age >65 years, chronic heart or pulmonary disease), a 4-factor model (adding prolonged mechanical ventilation), and an 11-factor model. Predictive performance was poor across all models, with the 3-factor model showing very low accuracy (Youden index, 0.08; $\kappa = 0.04$) and the 4-factor and 11-factor models demonstrating only modest improvements (Youden index, 0.12 and 0.16; $\kappa = 0.06$ and 0.07, respectively).

These findings indicate that simply counting risk factors is insufficient to accurately identify patients at high risk of reintubation. Accordingly, in this meta-analysis, we adopted an alternative definition of high risk – based on an observed reintubation rate $\geq 10\%$ in either the HFNC or NIV group – rather than relying solely on predefined clinical risk factors. This approach aimed to reduce heterogeneity and more accurately reflect real-world risk when comparing the preventive effects of HFNC and NIV in post-extubation patients.

HFNC offers both clinical advantages (including improved patient comfort and ease of use) and physiological benefits, such as enhanced oxygenation, alveolar recruitment, humidification and heating, improved secretion clearance, and reduction of anatomical dead space [37]. These effects may help prevent deterioration in lung function and reduce the need for tracheal intubation [38]. Compared with conventional oxygen therapy (COT) and NIV, HFNC is generally better tolerated and associated with greater patient comfort. However, its capacity to reduce respiratory muscle workload in acute respiratory failure (ARF) may be inferior to that of NIV [1].

In patients who respond poorly to HFNC or NIV, prolongation of noninvasive respiratory support may delay intubation and increase in-hospital mortality [39]. In such cases, a combined strategy – such as NIV alternating with HFNC – may be more appropriate. Indeed, in mechanically ventilated patients at high risk of extubation failure, the combined use of HFNC and NIV after extubation has been shown to significantly reduce the risk of reintubation compared with HFNC alone [31]. However, the role of combined HFNC+NIV strategies in post-extubation management requires further investigation.

This study fulfills most methodological criteria recommended for systematic reviews and meta-analyses [40]. Nevertheless, several limitations should be acknowledged. First, HFNC and NIV settings varied across studies, potentially influencing outcomes. Second, all included trials were unblinded due to the nature of the interventions, introducing potential performance bias. Third, baseline PaCO₂ and pH values differed between studies. Fourth, neither

the included trials nor this meta-analysis differentiated between hypercapnic and hypoxemic post-extubation patients. As a result, a potential inferiority of HFNC in hypercapnic patients may have been diluted by apparent equivalence in hypoxemic populations.

Fifth, some studies focused on specific patient subgroups (e.g., obese patients or those undergoing cardiothoracic surgery), which may limit external validity. Sixth, the use of a $\geq 10\%$ reintubation rate threshold to define “high risk” may be arbitrary and insufficiently discriminatory, potentially introducing selection bias and limiting clinical applicability. Seventh, substantial heterogeneity and evidence of publication bias were observed for some outcomes, reducing overall certainty.

Eighth, defining “high risk of reintubation” based on observed event rates in study arms introduces conceptual limitations, as this approach relies on post-randomization outcomes rather than baseline patient characteristics. This may preferentially select studies with poorer outcomes rather than truly high-risk populations at the time of extubation. Ninth, considerable clinical heterogeneity exists across trials with respect to patient populations, indications for mechanical ventilation, underlying respiratory physiology, and extubation contexts. Subgroup analysis based solely on baseline PaCO₂ is unlikely to capture this complexity, suggesting that treatment effects may be context-dependent rather than uniform.

Conclusions

Compared with NIV, HFNC was not associated with an increased risk of reintubation or mortality in post-extubation patients at high risk. However, important uncertainties remain regarding the relative effectiveness of HFNC and NIV in different physiological subgroups, particularly hypercapnic vs hypoxemic respiratory failure.

Given variability in definitions and study populations, these findings cannot be directly translated into bedside decision-making for individual patients. Future studies should focus on refining patient selection criteria and evaluating combined strategies, such as HFNC plus NIV, to optimize post-extubation respiratory support.

Funding

No funding was received for this work.

Conflict of interests

None of the authors has a conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at <https://doi.org/10.1016/j.arbres.2026.04.006>.

References

- [1] Oczkowski S, Ergan B, Bos L, Chatwin M, Ferrer M, Gregoretti C, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. *Eur Respir J* 2022;59:2101574.
- [2] Maggiore SM, Battilana M, Serano L, Petrini F. Ventilatory support after extubation in critically ill patients. *Lancet Respir Med* 2018;6:948–62.
- [3] Rochweg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017;50:1602426.
- [4] Maia IS, Kawano-Dourado L, Tramuja L, de Oliveira NE, Souza RN, Signorini DF, et al. High-flow nasal oxygen vs noninvasive ventilation in patients with acute respiratory failure: the RENOvATE randomized clinical trial. *JAMA* 2025;333:875–90.
- [5] Fernando SM, Tran A, Sadeghirad B, Burns KEA, Fan E, Brodie D, et al. Noninvasive respiratory support following extubation in critically ill adults:

- a systematic review and network meta-analysis. *Intensive Care Med* 2022;48:137–47.
- [6] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9. W64.
- [7] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366, 14898.
- [8] Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64–75.
- [9] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
- [10] De Jong A, Bignon A, Stephan F, Godet T, Constantin JM, Asehounne K, et al. Effect of non-invasive ventilation after extubation in critically ill patients with obesity in France: a multicentre, unblinded, pragmatic randomised clinical trial. *Respir Med* 2023;11:530–9.
- [11] Fang G, Wan Q, Tian Y, Jia W, Luo X, Yang T, et al. Comparative study on pros and cons of sequential high-flow nasal cannula and non-invasive positive pressure ventilation immediately following early extubated patients with severe respiratory failure due to acute exacerbations of chronic obstructive pulmonary disease. *Zhonghua wei zhong bing ji jiu yi xue* 2021;33:1215–20.
- [12] Hernández G, Vaquero C, Colinas L, Cuena R, González P, Canabal A, et al. Effect of postextubation high-flow nasal cannula vs noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. *JAMA* 2016;316:1565–74.
- [13] Hernández G, Paredes I, Moran F, Buj M, Colinas L, Rodríguez ML, et al. Effect of postextubation noninvasive ventilation with active humidification vs high-flow nasal cannula on reintubation in patients at very high risk for extubation failure: a randomized trial. *Intensive Care Med* 2022;48:1751–9.
- [14] Hernández G, Diant J, Paredes I, Moran F, Marquez M, Calle A, et al. Humidified noninvasive ventilation versus high-flow therapy to prevent reintubation in patients with obesity: a randomized clinical trial. *Am J Respir Crit Care Med* 2025;211:222–9.
- [15] Ketan PS, Kumar R, Aj M, Ish P, Chakrabarti S, Gupta NK, et al. Post-extubation high-flow nasal cannula oxygen therapy versus non-invasive ventilation in chronic obstructive pulmonary disease with hypercapnic respiratory failure. *Monaldi Arch Chest Dis* 2023;94.
- [16] Kumari N, Kumari B, Kumar S, Arun N, Kumari R. Effectiveness of high flow nasal cannula (HFNC) versus bilevel positive airway pressure (BiPAP) in preventing tracheal reintubation in patients with high risk of extubation failure in intensive care unit – a randomised comparative trial. *Indian J Anaesth* 2024;68:246–53.
- [17] Stéphan F, Barrucand B, Petit P, Rézaiguia-Delclaux S, Médard A, Delannoy B, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA* 2015;313:2331–9.
- [18] Tan D, Walline JH, Ling B, Xu Y, Sun J, Wang B, et al. High-flow nasal cannula oxygen therapy versus non-invasive ventilation for chronic obstructive pulmonary disease patients after extubation: a multicenter, randomized controlled trial. *Crit Care* 2020;24:489.
- [19] Tongyoo S, Tantibundit P, Daorattanachai K, Viarasilpa T, Permpikul C, Udompanturak S. High-flow nasal oxygen cannula vs. noninvasive mechanical ventilation to prevent reintubation in sepsis: a randomized controlled trial. *Ann Intensive Care* 2021;11:135.
- [20] Tseng CW, Chao KY, Wu HL, Lin CC, Hsu HS. Effectiveness of high-flow nasal cannulae compared with noninvasive positive-pressure ventilation in preventing reintubation in patients receiving prolonged mechanical ventilation. *Sci Rep* 2023;13:4689.
- [21] Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. Clin Infect Dis* 2016;63:e61–111.
- [22] Hernández G, Vaquero C, Ortiz R, Colinas L, de Pablo R, Segovia L, et al. Benefit with preventive noninvasive ventilation in subgroups of patients at high-risk for reintubation: a post hoc analysis. *J Intensive Care* 2022;10:43.
- [23] Akella P, Voigt LP, Chawla S. To wean or not to wean: a practical patient focused guide to ventilator weaning. *J Intensive Care Med* 2022;37:1417–25.
- [24] Shah NM, Hart N, Kaltsakas G. Prolonged weaning from mechanical ventilation: who, what, when and how? *Breathe (Sheff)* 2024;20, 240122.
- [25] Pham T, Heunks L, Bellani G, Madotto F, Aragao I, Beduneau G, et al. Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre, prospective, observational cohort study. *Respir Med* 2023;11:465–76.
- [26] Burns KEA, Rizvi L, Cook DJ, Lebovic G, Dodek P, Villar J, et al. Ventilator weaning and discontinuation practices for critically ill patients. *JAMA* 2021;325:1173–84.
- [27] Hernández G, Hill NS. How to prevent postextubation respiratory failure. *Curr Opin Crit Care* 2025;31:93–100.
- [28] Rochwerg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med* 2020;46:2226–37.
- [29] Thille AW, Boissier F, Ben Ghezala H, Razazi K, Mekontso-Dessap A, Brun-Buisson C. Risk factors for and prediction by caregivers of extubation failure in ICU patients: a prospective study. *Crit Care Med* 2015;43:613–20.
- [30] Casey JD, Vaughan EM, Lloyd BD, Billas PA, Jackson KE, Hall EJ, et al. Protocolized postextubation respiratory support to prevent reintubation: a randomized clinical trial. *Am J Respir Crit Care Med* 2021;204:294–302.
- [31] Thille AW, Muller G, Gacouin A, Coudroy R, Decavèle M, Sonneville R, et al. Effect of postextubation high-flow nasal oxygen with noninvasive ventilation vs high-flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: a randomized clinical trial. *JAMA* 2019;322:1465–75.
- [32] Ferrer M, Sellarés J, Valencia M, Carrillo A, Gonzalez G, Badia JR, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet* 2009;374:1082–8.
- [33] Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;39:2612–8.
- [34] Rodríguez Villamizar P, Thille AW, Márquez Doblas M, Frat JP, Leal Sanz P, Alonso E, et al. Best clinical model predicting extubation failure: a diagnostic accuracy post hoc analysis. *Intensive Care Med* 2025;51:106–14.
- [35] Hernández Martínez G, Rodríguez P, Soto J, Caritg O, Castellví-Font A, Mari-blanca B, et al. Effect of aggressive vs conservative screening and confirmatory test on time to extubation among patients at low or intermediate risk: a randomized clinical trial. *Intensive Care Med* 2024;50:258–67.
- [36] Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G, et al. Effect of postextubation high-flow nasal cannula vs conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. *JAMA* 2016;315:1354–61.
- [37] Chidekel A, Zhu Y, Wang J, Mosko JJ, Rodríguez E, Shaffer TH. The effects of gas humidification with high-flow nasal cannula on cultured human airway epithelial cells. *Pulm Med* 2012;2012, 380686.
- [38] Ricard JD, Roca O, Lemiale V, Corley A, Braunlich J, Jones P, et al. Use of nasal high flow oxygen during acute respiratory failure. *Intensive Care Med* 2020;46:2238–47.
- [39] Renda T, Corrado A, Iskandar G, Pelaia G, Abdalla K, Navalesi P. High-flow nasal oxygen therapy in intensive care and anaesthesia. *Br J Anaesth* 2018;120:18–27.
- [40] Liberati A, Altman DG, Tetzlaff J, Mulrow G, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W65–94.