

NIV vs HFNC in Respiratory Failure

EVIDENCE AND CLINICAL APPLICATION

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Respiratory Failure and Non-Invasive Respiratory Support

Primary indication for medical ICU admission in ~ 20% cases^{1,2}

Non-Invasive respiratory support (NRS) modalities:

- Initial management strategy
- HFNC, NIV, CoT

Goals of NRS Therapy:

- Increase oxygenation
- Reduce work of breathing
- Improve ventilation and CO₂ washout
- Reduce dyspnoea and discomfort
- Avoid Intubation
- Prevent mortality

1. Vincent JK et al. JAMA.2009;302:2323-9

2. Divatia JV. Indian J Crit Care Med 2016;20:216-25

Outline

Physiological Effect of HFNC and NIV

Device Comparison

Evidence in:

- Hypoxemic Respiratory Failure
- Immunocompromised patients
- Hypercapnic Respiratory Failure
- Post-Extubation Support

Conventional Oxygen Therapy v/s HFNC

Mechanistic Comparison

Parameter	Conventional Low-Flow Oxygen (Nasal Prongs/ Face Mask)	High-Flow Nasal Cannula (HFNC)
Device type	Low or high-flow oxygen delivery device	High-flow oxygen delivery system
O ₂ delivery	Oxygen delivered at flow lower than patient inspiratory demand , so room air entrainment occurs	Meets and/or exceeds patient's inspiratory demand, no entrainment of room air
Flow range	1–15L/min (< Inspiratory demand)	Up to 60 L/min (≥ Inspiratory demand)
FiO ₂ range	~ 24 – ~90% depends on flow breathing pattern and device used	21–100% , precisely adjustable
Humidification	Usually minimal or cold bubble humidification ; No temperature control	Active heated humidification at controlled temperature
Dead Space Washout (DSW)	Minimal	Significant nasopharyngeal DSW

Physiological Effects of HFNC

Dead Space Washout

- Nasopharyngeal dead space CO₂ washout
- O₂ Reservoir and ↓ re-breathing of CO₂

Low level PEEP

- Mouth Open - 1.7 ± 0.82 @ 50L/min
- Mouth Closed – 3.3 ± 1.1 @ 50L/min
- ~0.7 cm H₂O per 10 L/min

Humidification and High Flow

- ↓ Meets/can exceed inspiratory demand
- ↓ Work of Breathing (diaphragmatic workload)

Airway Physiology

- Improves mucociliary clearance
- Reduced mucus plug risk and airway resistance

IMPACT: Reduces work of breathing and prevents CO₂ rebreathing

D'Cruz RF et al. *Breathe*. 2020;16:200224

Goligher EC et al. *Am J Respir Crit Care Med*. 2017;195:1128-1131

Physiological Effects of NIV

Improves Ventilation and Gas Exchange

- Increases tidal volume (V_t)
- $\uparrow$ O₂ delivery to alveoli and $\uparrow$ CO₂ elimination

Improves Ventilation-Perfusion Mismatch

- PS delivered $V_t \rightarrow$ recruits collapsed alveoli
- PEEP prevents de-recruitment

Reduces Work of Breathing

- $\downarrow$ Inspiratory muscle workload
- PEEP counteracts iPEEP

Improves Cardiovascular Function

- $\downarrow$ venous return
- $\downarrow$ LV afterload

IMPACT: Reduces respiratory rate and Inspiratory effort

Mechanistic and Physiological Comparison

Mechanism / Effect	HFNC	NIV
Primary mechanism	High flow washes out nasopharyngeal dead space and provides stable FiO ₂	Pressure support ventilation actively assists inspiration
Dead space washout	Major mechanism – clears CO ₂ from upper airway	Minimal effect
Inspiratory assistance	None (patient generates full Vt)	Yes – IPAP augments tidal volume
Effect on tidal volume	Minimal direct increase	Significant increase due to pressure support
Alveolar recruitment	Minimal(flow-dependent PEEP)	Recruitment via PEEP
CO₂ clearance	Indirect via dead-space washout	Direct via increased alveolar ventilation

Why compare HFNC and NIV

Both are commonly available options with overlapping indications

Different mechanisms and physiological effects

Same Goal:

Avoiding intubation

Prevent Mortality

Incorrect selection may lead to:

Treatment failure

Delayed Intubation

Adverse Outcomes

Hypoxemic Respiratory Failure

High-Flow Nasal Cannula Compared With Noninvasive Positive Pressure Ventilation in Acute Hypoxic Respiratory Failure: A Systematic Review and Meta-Analysis



Research Question

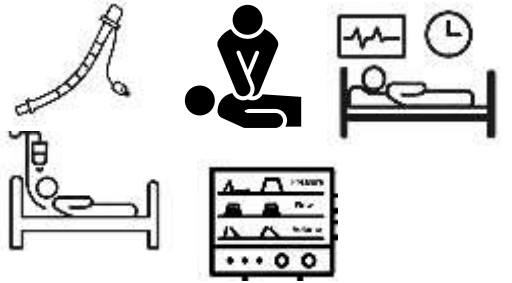
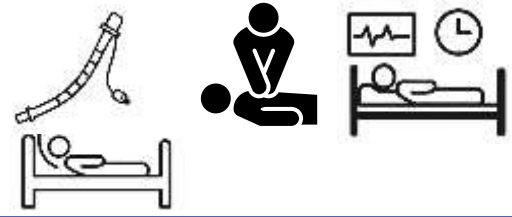
Component	Description
Population	Adults with acute hypoxemic respiratory failure (AHRF)
Intervention	High-Flow Nasal Cannula (HFNC)
Comparator	Non-invasive positive pressure ventilation (NIPPV)
Outcomes	Intubation, mortality, ICU LOS, hospital LOS

PROSPERO Registered and PRISMA Checklist provided

Literature Search: MEDLINE, EMBASE., Cochrane, CIHNA databases ; ?Grey literature

Analysis: 9 RCTs ; n=1539

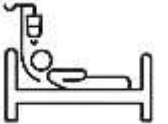
Study Characteristics

Study	NIV & Settings (P in cm H2O)	Comparator & Settings	Inclusion Criteria	Outcomes
Elagamy et al. 2021 n = 76	Full Face Mask PS/PEEP: 8/5	HFNC Settings not Described	immunocompromised T1RF	
Target: SpO2 ≥92%				
Frat et al. 2015 n = 216 (310)	Full Face Mask VT 7 - 10 mL/kg PEEP 2 - 10	HFNC 50 L/min, FiO2 1.0 ?P-SILI	T1RF with SpO2 < 95% on FiO2 50% via FM	
Target: SpO2 ≥92%				
Perkins et al. 2021 ; n = 791 RECOVERY-RS	Full Face Mask CPAP PEEP: 5 - 10	HFNC Flow upto 60L/min	COVID-19 + FiO2>40% + SaO2<94%	
Target: SpO2 ≥ 92-96%				

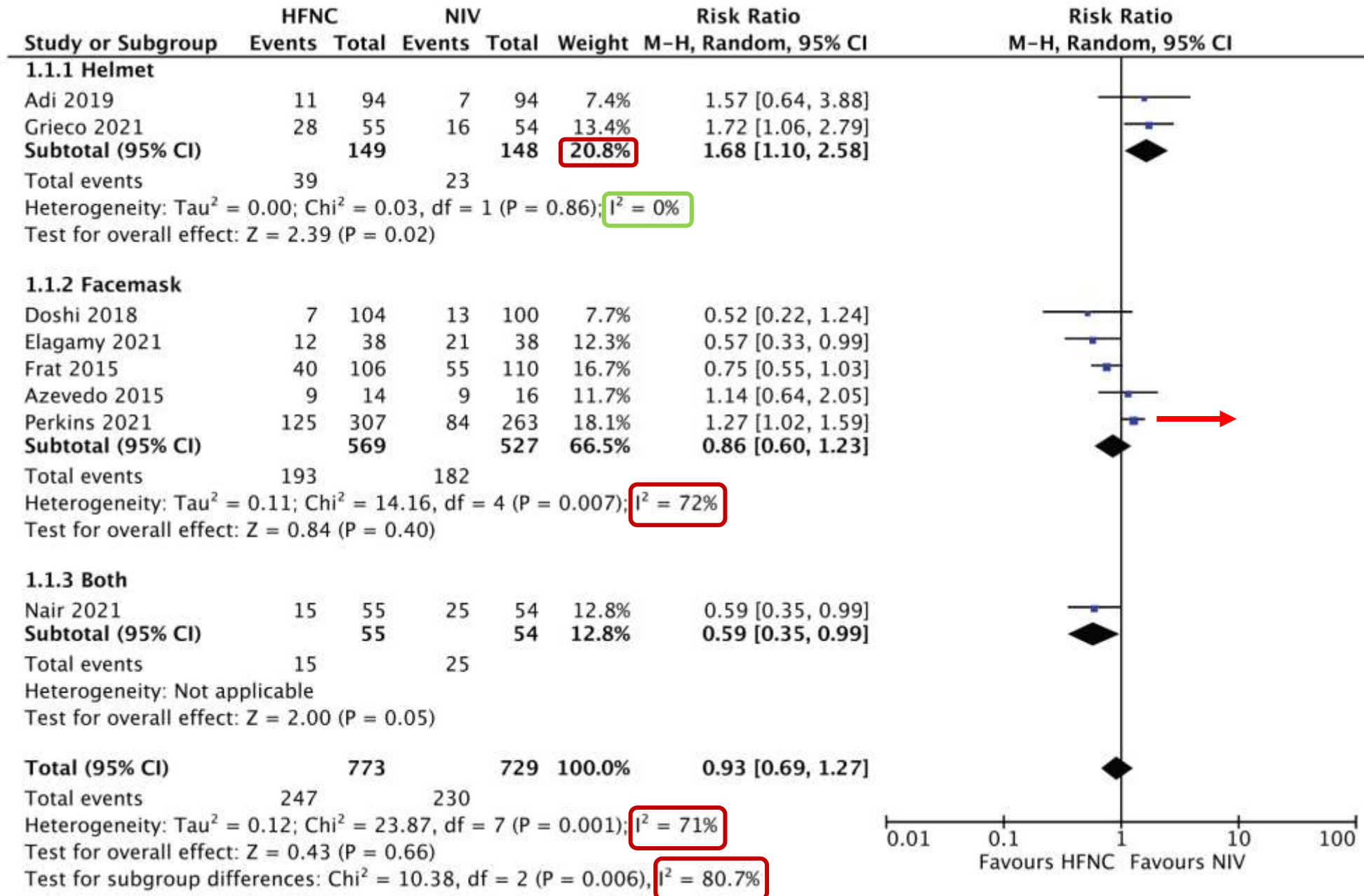
Study Characteristics...

Study	NIV & Settings (P in cm H2O)	Comparator & Settings	Inclusion Criteria	Outcomes
 Grieco et al. 2020 n = 15	Helmet NIV PS: 8-10, till 20 PEEP: 10-12	HFNC Not Described	ED - T1RF with RR >25, SpO2 <90%	
 Nair et al. 2021 n = 104 AIIMS DELHI	Full Face Mask & Helmet NIV PS 10–20, PEEP 5 - 10, FiO2 0.5 - 1.0, Target: SpO2 >94%	HFNC 50 L/min, FiO2 1.0 then 30-60 L/min	COVID-19 ARDS failing CoT	
 Grieco et al. 2021 n = 109	Helmet NIV PS 10 - 12, PEEP 10- 12 Target: SpO2 92-98%	HFNC 60 L/min 34-37°C	Covid ARDS with P/F <200 Intubation Rate, Mortality, ICU LOS, Complications	

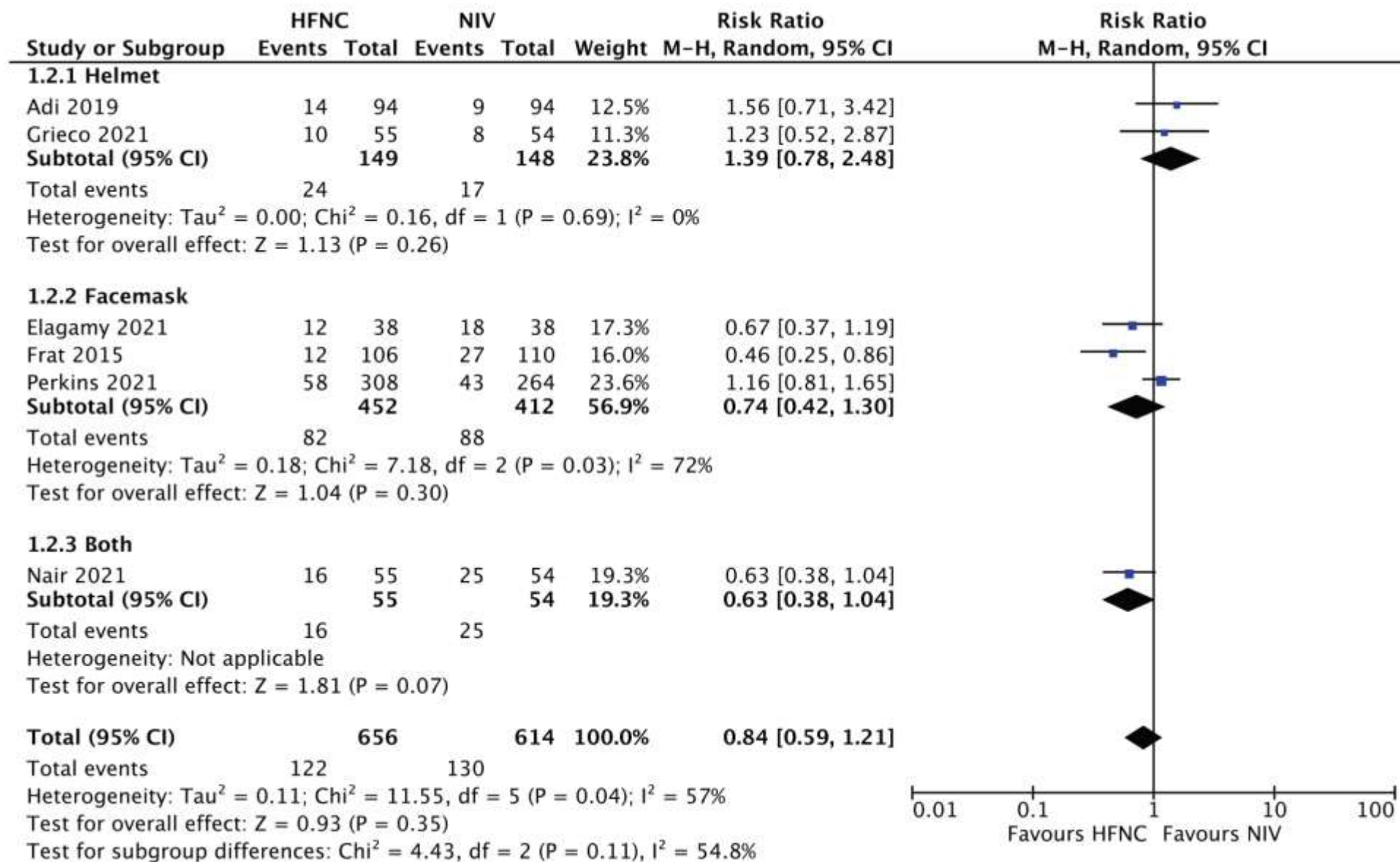
Study Characteristics...

	Study	NIV & Settings (P in cm H2O)	Comparator & Settings	Inclusion Criteria	Outcomes
●	Adi et al. 2019 n = 188	Helmet CPAP Settings not Described	HFNC Settings not Described	ED Acute Heart Failure	  
●	Azevedo et al. 2015 n = 30	Full Face Mask Settings not Described	HFNC Not Described	ED – T1RF with SpO2 < 95% with FiO2 50% via FM	
●	Doshi et al. 2018 n = 204	Full Face Mask PS/PEEP: 10-20/5-10 FiO2 1.0	HFNC Flow 35–40 L/min, 35–37°C, FiO2 1.0	ED – T1RF	  
		Target RR <25; SpO2 >88			

Intubation Outcomes: ? Neutral



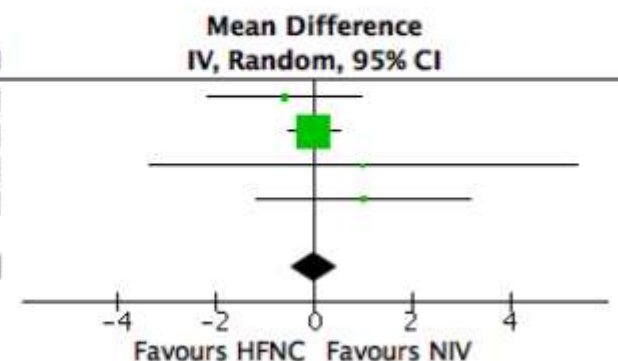
No Mortality Difference



No Length of Stay Benefit

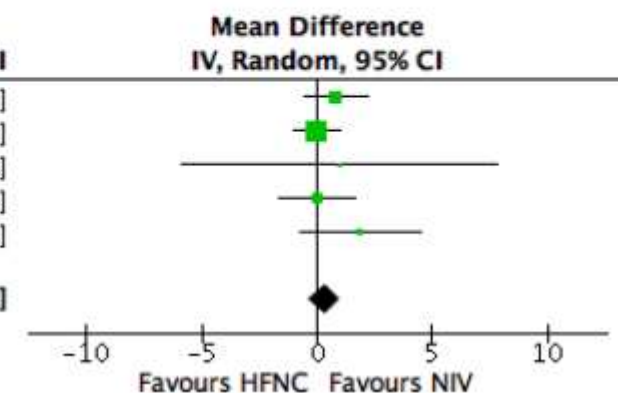
ICU Length of Stay

Study or Subgroup	HFNC			NIV			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Doshi 2018	3.3	3.7	48	3.9	4.1	47	9.5%	-0.60 [-2.17, 0.97]
Elagamy 2021	4	0.74	38	4	1.48	38	84.4%	0.00 [-0.53, 0.53]
Grieco 2019	10	13.3	55	9	9.63	54	1.2%	1.00 [-3.35, 5.35]
Perkins 2021	10.5	15.6	414	9.5	15.6	377	4.9%	1.00 [-1.18, 3.18]
Total (95% CI)			555			516	100.0%	0.00 [-0.48, 0.49]
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.57$, $df = 3$ ($P = 0.67$); $I^2 = 0\%$								
Test for overall effect: $Z = 0.02$ ($P = 0.98$)								



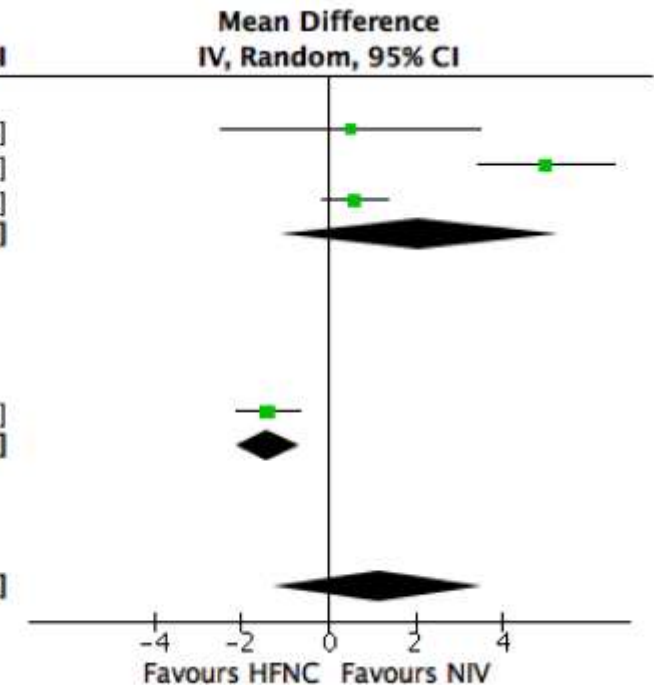
Hospital Length of Stay

Study or Subgroup	HFNC			NIV			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Doshi 2018	6.8	5.7	104	6	4.4	100	24.4%	0.80 [-0.59, 2.19]
Elagamy 2021	5	0.74	38	5	2.96	38	50.3%	0.00 [-0.97, 0.97]
Grieco 2021	22	22.96	55	21	11.9	54	1.0%	1.00 [-5.85, 7.85]
Nair 2021	9	4.4	54	9	4.4	55	17.4%	0.00 [-1.65, 1.65]
Perkins 2021	18.3	20	414	16.4	17.5	377	6.9%	1.90 [-0.71, 4.51]
Total (95% CI)			665			624	100.0%	0.34 [-0.35, 1.03]
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.46$, $df = 4$ ($P = 0.65$); $I^2 = 0\%$								
Test for overall effect: $Z = 0.96$ ($P = 0.34$)								



Similar Comfort

Study or Subgroup	HFNC			NIV			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
1.5.1 Helmet								
Adi 2019	4	11.3	94	3.5	9.4	94	19.8%	0.50 [-2.47, 3.47]
Grieco 2019	8	2.2	15	3	2.2	15	25.2%	5.00 [3.43, 6.57]
Grieco 2021	2.5	2	55	1.9	2	54	27.5%	0.60 [-0.15, 1.35]
Subtotal (95% CI)			164			163	72.5%	2.09 [-1.11, 5.29]
Heterogeneity: $\tau^2 = 7.06$; $\chi^2 = 24.79$, $df = 2$ ($P < 0.00001$); $I^2 = 92\%$								
Test for overall effect: $Z = 1.28$ ($P = 0.20$)								
1.5.2 Facemask								
Frat 2015	2.9	2.6	106	4.3	2.9	110	27.5%	-1.40 [-2.13, -0.67]
Subtotal (95% CI)			106			110	27.5%	-1.40 [-2.13, -0.67]
Heterogeneity: Not applicable								
Test for overall effect: $Z = 3.74$ ($P = 0.0002$)								
Total (95% CI)			270			273	100.0%	1.14 [-1.28, 3.56]
Heterogeneity: $\tau^2 = 5.38$; $\chi^2 = 55.01$, $df = 3$ ($P < 0.00001$); $I^2 = 95\%$								
Test for overall effect: $Z = 0.92$ ($P = 0.36$)								
Test for subgroup differences: $\chi^2 = 4.35$, $df = 1$ ($P = 0.04$), $I^2 = 77.0\%$								



Strengths & Fallacies

Methodological Strengths

- RCTs with head-to-head comparisons
- Subgroup analysis

Pooling Diseases and Interventions

- Pooling of distinct diseases under AHRF
- Treated NIV as a single intervention
- Power calculation not done ($n \sim 1200 - 2400$)

Intubation Analysis

- Studied as binary outcome
- No time to event analysis risking delayed intubation bias

Co-interventions

- Not accounted for effect of anti-microbial therapy, steroids, fluids

Anchor Trials

- Recovery-RS - used CPAP
- Florali – NIV+HFNC vs HFNC ; not NIV vs HFNC

Conclusion

Intubation – No difference ; Low Certainty

Mortality – No difference ; Very Low Certainty

ICU LoS – No difference ; Moderate Certainty

Hospital LoS – No difference ; Low Certainty

Dyspnoea – No difference ; Very Low Certainty

Landmark Trials

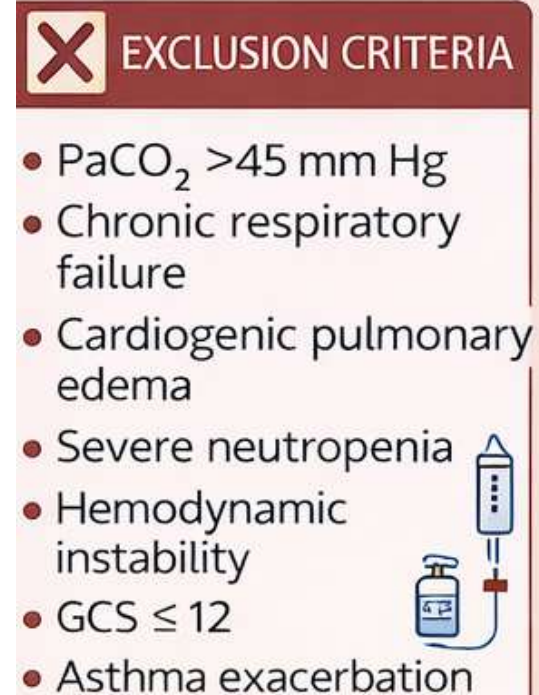
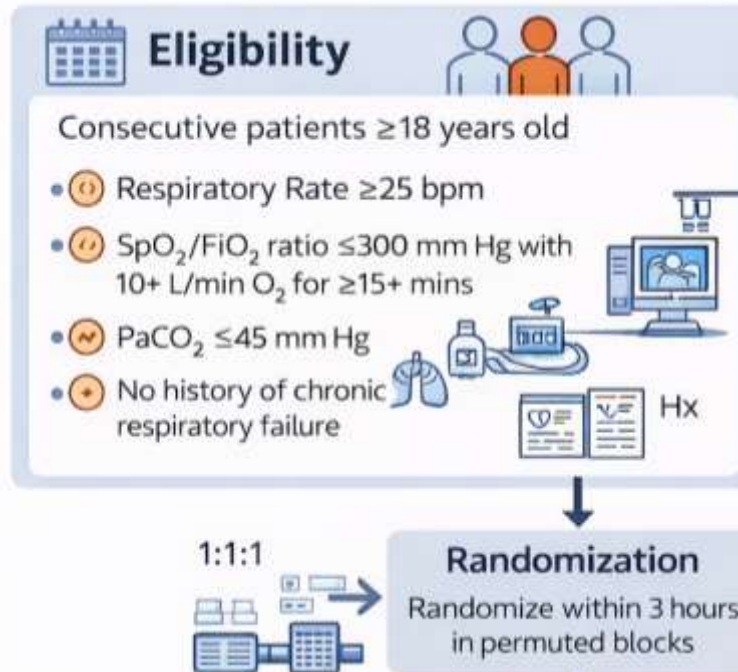
The NEW ENGLAND JOURNAL of MEDICINE

FLORALI TRIAL

JUNE 4, 2015

VOL. 372 NO. 23

High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure



Methodology

Standard Oxygen Therapy	High-Flow Oxygen Therapy	Noninvasive Ventilation
 Nonrebreather mask ≥ 10 L/min O_2 • FiO_2 titrated maintain $SpO_2 > 92\%$	 High-flow cannula 50 L/min heated, humidified O_2 FiO_2 1.0 initially, then reduced maintain $SpO_2 > 92\%$ • Continued ≥ 2 days	 Noninvasive ventilator PS, 7-10 ml/kg PEEP, 2-10 cm H_2O FiO_2 titrated >8 hrs/day for >2 days • Fed with high-flow O_2 between sessions

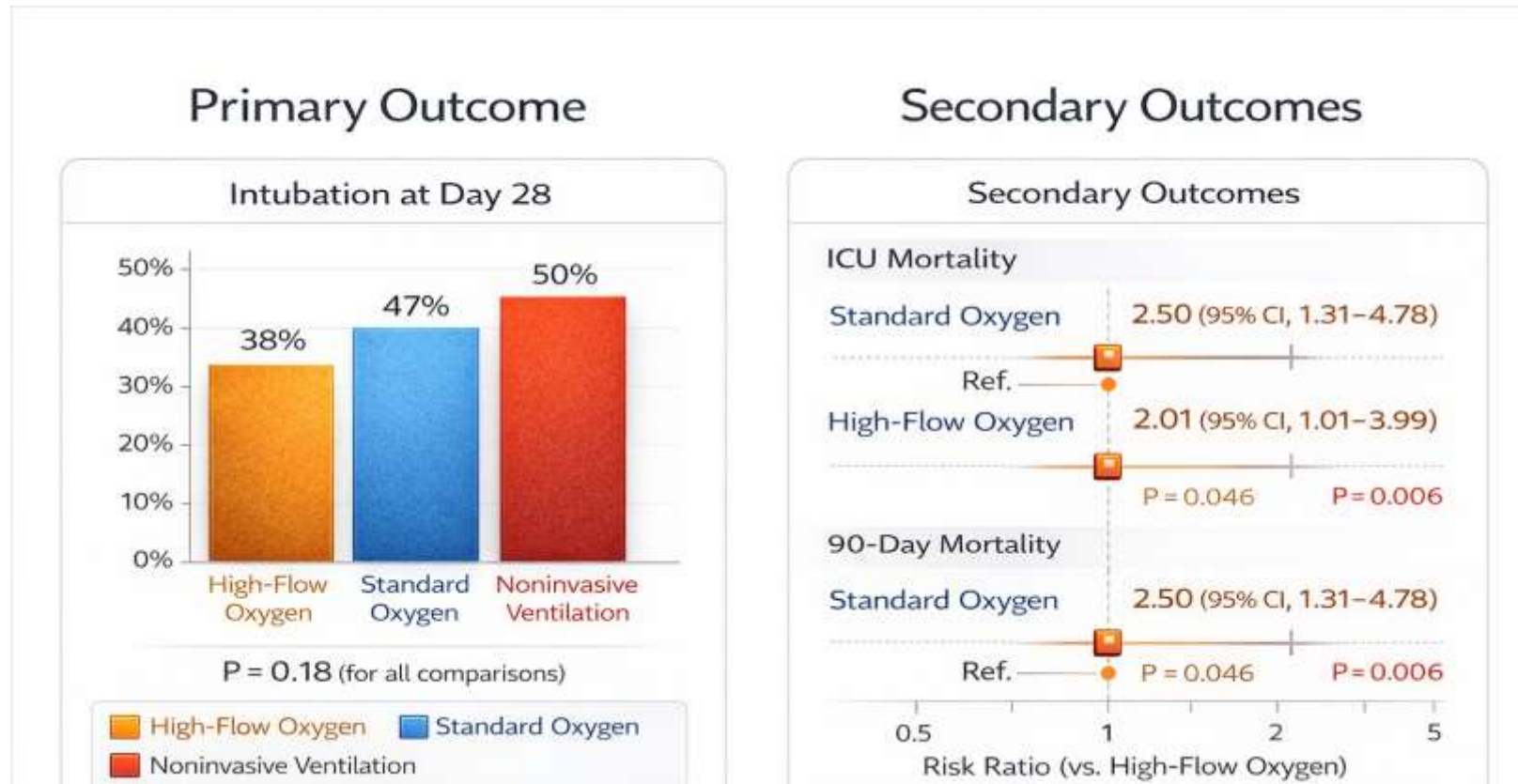
Primary Outcome

- Endotracheal intubation within 28 days of randomization

Secondary Outcome

- All cause mortality at 90 days
- Ventilator-free days at 28 days (IMV only)

Mortality benefit but similar rate of intubation



Interpretation

CORRESPONDENCE

Inderpaul S. Sehgal, M.D., D.M.

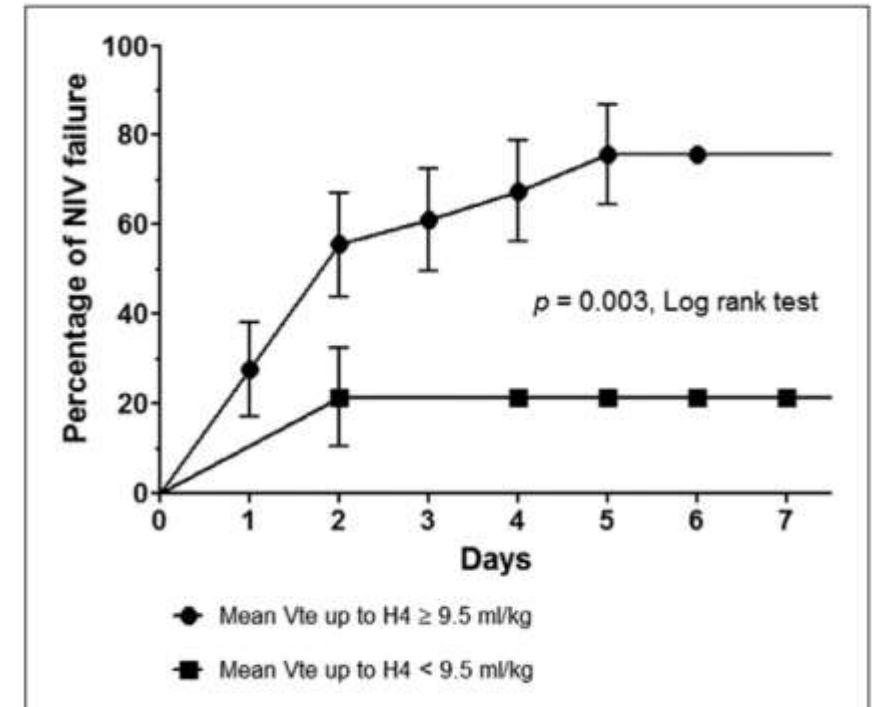
Sahajal Dhoooria, M.D., D.M.

Ritesh Agarwal, M.D., D.M.

Postgraduate Institute of Medical Education and Research
Chandigarh, India

~~HFNC offers mortality benefit without reducing intubation rates~~

- Suboptimal duration of NIV (median: 8 hrs/day in first 2 days)
- Assumed intubation rate (60%) > Observed Rate (44.8%)
Underpowered for primary objective
- NIV Group
 - VT of 9.2 ± 3 ml/kg – Mayb have induced P-SILI
 - Received HFNC between NIV sessions instead of SoC
- Mortality was secondary outcome – Underpowered, needs confirmation
- HFNC – Variable PEEP



Carteaux et al. Crit. Care Med. 2016

Effect of **Helmet Noninvasive Ventilation** vs **High-Flow Nasal Oxygen** on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure

The HENIVOT Randomized Clinical Trial

Inclusion

- Covid Pneumonia with T1RF in ICU
- ICU Stay < 24 hours
- $P/F \leq 200$
- $pCO_2 < 45$ mmHg

Exclusion

- AE of chronic respiratory failure
- ADHF (NYHA > II or LVEF < 50%)
- CKD with Pulmonary Edema

Superiority trial ; Expected improvement with helmet NIV – 25% increase (11.6 vs 14.5) in respiratory support free days

Intervention

HFNC: Flow 60L/min → Titrated to maximum tolerated flow and FiO₂ titrated to SpO₂ 92 – 98%

Weaning: Flow reduced if FiO₂ < 40%, once flow was 10L/min → Switched to Venturi Mask or Nasal Prongs

Minimum duration: 48 hours

USE OF NIV NOT PERMITTED

NIV: PS 10 – 12 with PEEP 10

FiO₂ titrated to SpO₂ 92 – 98%

Weaning: Once FiO₂ < 40%, PS and PEEP reduced to PS/PEEP 8/8 → Switched to Venturi mask or HFNC

Minimum duration: 48 hours

HFNC use allowed

Results

Outcome	No. (%)		Absolute or mean difference (95% CI) ^b	Odds ratio (95% CI)	P value ^c
	Helmet noninvasive ventilation (n = 54) ^a	High-flow nasal oxygen (n = 55) ^a			
Primary outcome					
Respiratory support-free days, median (IQR) ^d	20 (0 to 25)	18 (0 to 22)	2 (−2 to 6)		.26
Secondary outcomes					
Intubation within 28 d from enrollment	16 (30)	28 (51)	−21 (−38 to −3)	0.41 (0.18 to 0.89)	.03
Intubation within 28 d from enrollment, after adjudication of intubation criteria by external experts	15 (28)	28 (51)	−23 (−39 to −5)	0.37 (0.17 to 0.82)	.02
Invasive ventilation-free days, median (IQR)					
28 d	28 (13 to 28)	25 (4 to 28)	3 (0 to 7)		.04
60 d	60 (43 to 60)	57 (19 to 60)	6 (−3 to 15)		.07
Mortality					
28 d	8 (15)	10 (18)	−3 (−17 to 11)	0.78 (0.28 to 2.16)	.80
60 d	13 (24)	12 (22)	2 (−13 to 18)	1.14 (0.46 to 2.78)	.82
In-intensive care unit mortality	11 (20)	14 (25)	−5 (−21 to 11)	0.75 (0.30 to 1.84)	.65
In-hospital mortality ^e	13 (24)	14 (25)	−1 (−17 to 15)	0.93 (0.39 to 2.22)	>.99
Duration of stay, median (IQR), d					
Intensive care unit	9 (4 to 17)	10 (5 to 23)	−6 (−13 to 1)		.22
Hospital	21 (14 to 30)	22 (13 to 44)	−6 (−14 to 1)		.47

hNIV possibly reduces intubation

IN FAVOUR

- Longer duration of hNIV compared to other trials which used Facemask NIV
- Awake proning imbalance (hNIV 0% vs HFNC 60%)

AGAINST

- Underpowered for secondary outcome
- Cannot be extrapolated to non-covid AHRF

Immunocompromised
with AHRF

Non-invasive Oxygenation Strategies in Immunocompromised Patients With Acute Hypoxemic Respiratory Failure: A Pairwise and Network Meta-Analysis of Randomized Controlled Trials

Zayed Y. et al. J Intensive Care Med. 2020;35:1216-1225

Research Question

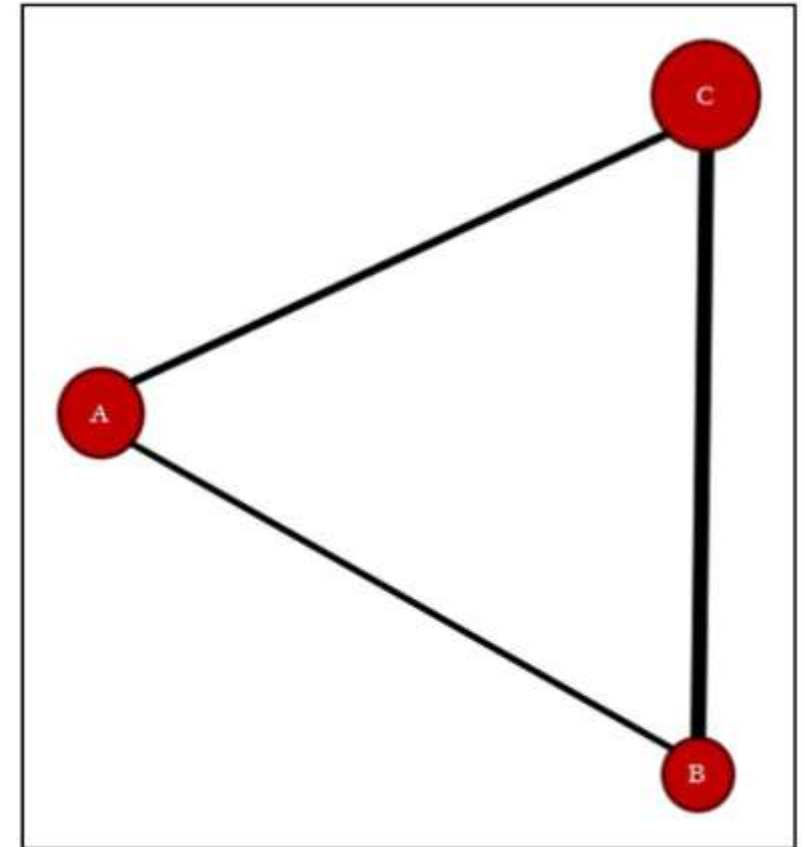
Component	Description
Population	Immunocompromised Adults with AHRF
Intervention	Non-invasive ventilation (NIV)
Comparator	High-Flow Nasal Cannula (HFNC) or Standard of Care
Outcomes	Intubation, mortality, ICU Infections

9 RCT, 1570 patients - SOC – 49% ; HFNC – 30% ; NIV – 21%

Network Geometry Diagram

Unit	Interpretation	Current Study
Node	A particular group of therapy	A – HFNC ; B – NIV ; C - SOC
Node Size	Sample size of that therapy arm	$C > A > B$
Edge	RCT between nodes	
Edge Thickness	No. of RCTs comparing nodes	$B-C > B-A > A-C$

*Indirect comparison by transitivity assumption
if no inconsistency*



Study Characteristics

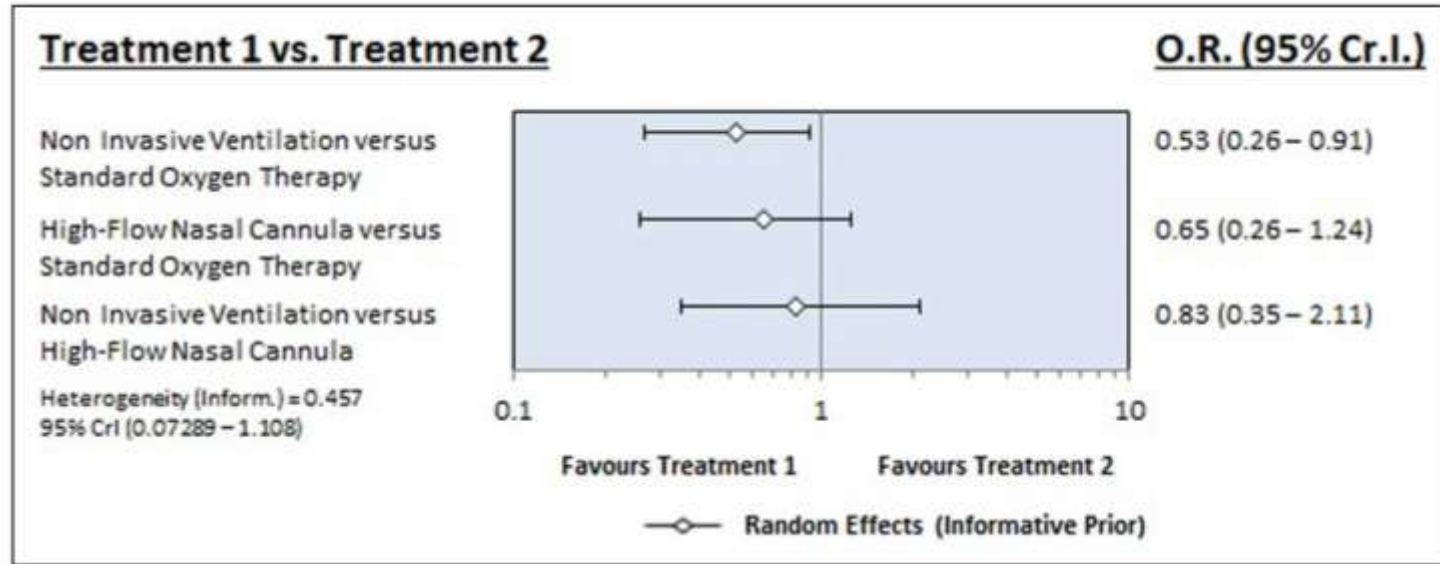
Study	Intervention	Comparator	N	Patients	Settings	Outcomes	Risk of Bias
Azouley et al 2018 (HIGH)	HFNC	Conventional Oxygen Therapy (CoT)	776	Immunocompromised AHRF (Pao ₂ <60 or RR >30/min)	Flow 50/min & FiO ₂ – 1.0 targetted to SpO ₂ >95%	Mortality, Intubation	Low
Frat et al 2015 (FLORALI)	NIV or HFNC	CoT	310 (216)	AHRF: P/F < 300	PS adjusted to Vt 7-10ml/kg HFNC 50L/min & FiO ₂ 1.0	Intubation, Mortality	Low
Gupta et al 2016	HFNC	NIV	20	Post liver transplant AHRF	EPAP/IPAP 5/10 HFNC 60L/min	Intubation	low
Lemiale et al 2017 (iVNIctus)	HFNC	Venturi Mask	100	Immunocompromised with SpO ₂ < 95% at FiO ₂ 0.4	PS to Vt 7-10ml/kg and PEEP 2-10	Mortality, Intubation	low

Study Characteristics

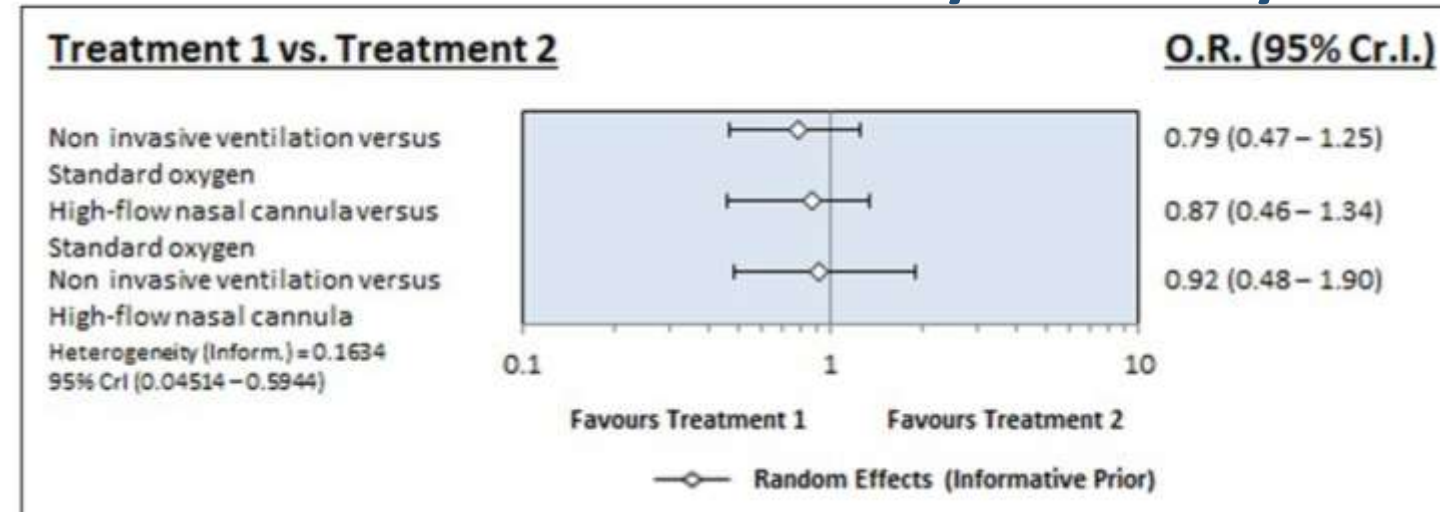
Study	Intervention	Comparator	N	Patients	Settings	Outcomes	Risk of Bias
Wermke et al 2012	NIV	CoT	78	HScT with P/F <300	PS/PEEP 15/7	Mortality, intubation	high
Squadrone	NIV	Venturi 50%	40	Hemat. Malignancies	CPAP 10 ; FiO2 50%	Mortality, intubation	Moderate
Hilbert et al 2001	NIV	CoT	72	Neutropenia Chemotherapy	Vt 7-10ml/Kg	Mortality, intubation	High
Antonelli et al 2001	NIV	CoT	40	Chemotherapy	Vt 8-10ml/Kg	intubation	High
Lemiale et al 2015	HFNC	Venturi Mask	374	Immunocompromised with SpO2 < 95% at FiO2 0.4	HFNC 60L/min x 2 hours	Intubation or NIV during the 2 hours	low

Intubation: NIV > SoC and NIV ~ HFNC

Results

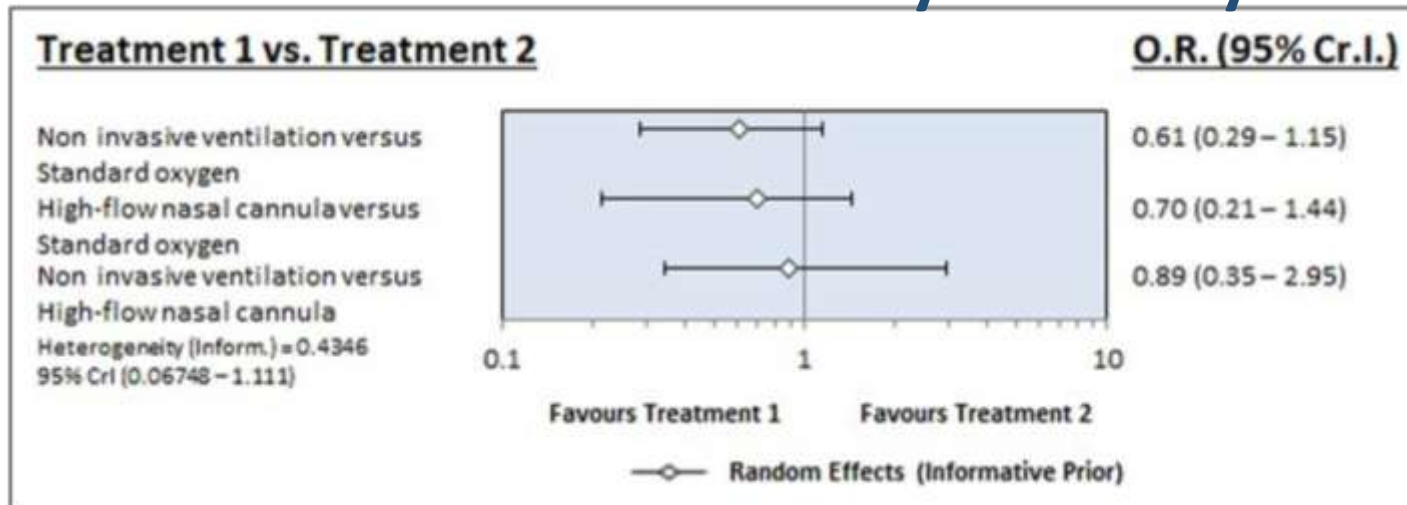


No difference in 28-Day Mortality

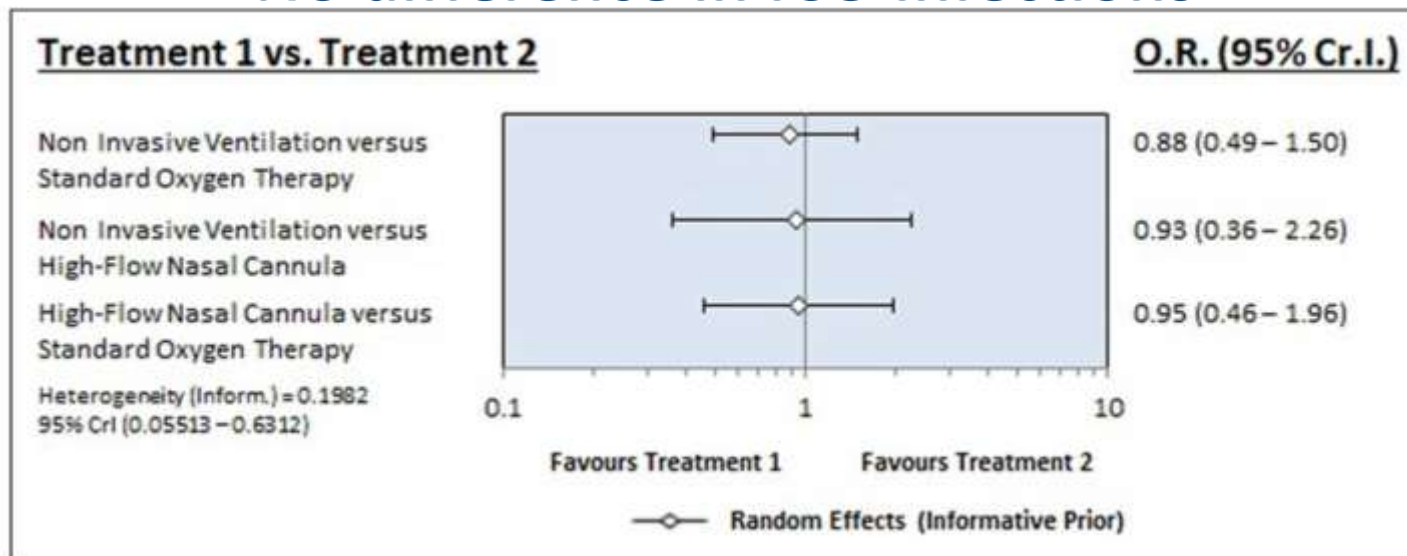


Results

No difference in 90-Day Mortality



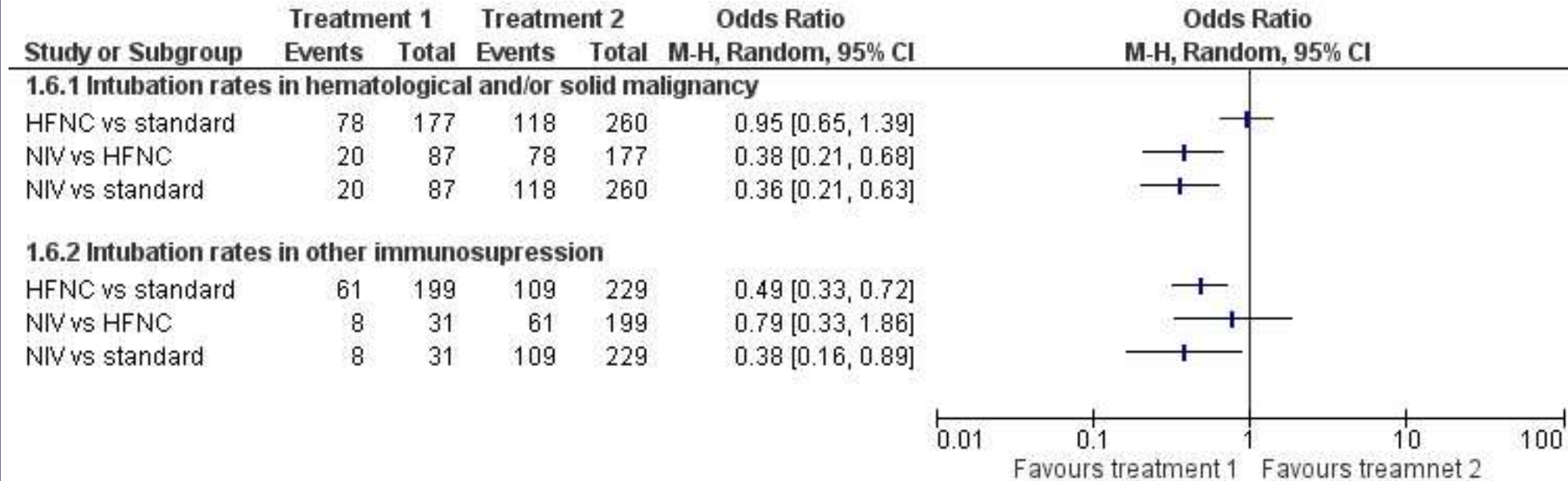
No difference in ICU Infections



Intubation Subgroup Analysis

Malignancy – NIV > HFNC ~SOC

Non-Malignancy – NIV~HFNC > SOC



Interpretation

NIV ~ HFNC except in malignancy subgroup

Small sample size

HFNC vs NIV – Mostly indirect evidence

2000 - 2018 – Practices and standard of care evolved

High-Flow nasal oxygen alone or alternating with non-invasive ventilation in immunocompromised critically ill with acute respiratory failure: FLORALI-IM Trial

Population: AHRF with RR > 25/min and P/F < 300 with CoT/HFNC/NIV

Immunosuppression criteria:

- Active solid cancer or haematological malignancy or allogeneic stem cell transplantation <5 years
- Leucopenia <1000 or neutropenia $\leq$ 500
- HIV-AIDS
- Systemic steroids $\geq$ 0.5 mg/kg /day of prednisone equivalent for at least 3 week
- Immunosuppressive or immunomodulatory drugs

Design

Exclusion criteria

- $p\text{CO}_2 > 50$ mm Hg
- Chronic lung disease
- Cardiogenic pulmonary Edema
- postoperative
- Shock with vasopressor dose > 0.3 $\mu\text{g/kg}$ per min
- GCS < 12

HFNO Group

flow rate of 60 L/min, or the highest tolerated

NIV Group

Treated with NIV alternating with HFNO

NIV initiated with a first session of at least 4 h until clinical improvement and then applied for a minimum duration of 12 h/day

PEEP – 8 ; PS – to target V_t 8ml/kg/PBW

RESULTS

	HFNO alone group (n=154)	NIV group (n=145)	Absolute or mean difference (95% CI)	p value
Primary outcome				
Mortality at day 28	56 (36%)	51 (35%)	1.2 (-9.6 to 11.9)	0.83
Secondary outcomes				
Intubation at day 28	78 (51%)	67 (46%)	4.4 (-6.8 to 15.5)	0.44
Mortality of intubated patients in the ICU	40/78 (51%)	43/67 (64%)	-	-
Mortality				
In the ICU	45 (29%)	49 (34%)	-4.6 (-15.0 to 5.9)	0.39
In hospital	63 (41%)	60 (41%)	-0.5 (-11.5 to 10.6)	0.93
At day 90	67 (44%)	63 (43%)	0.1 (-11.1 to 11.2)	0.99
At day 180	76 (49%)	70 (48%)	1.1 (-10.1 to 12.3)	0.85
Cause of death at day 28	..	..	..	0.95
Withdrawal or withholding of treatments	22/56 (39%)	21/51 (41%)	-	..
Denied intubation	3/22 (14%)	5/22 (23%)	..	..
Related to the underlying disease	9/56 (16%)	10/51 (20%)	-	..
Refractory shock	6/56 (11%)	5/51 (10%)	-	..
Refractory hypoxaemia	4/56 (7%)	4/51 (8%)	-	..
Sudden cardiac arrest	5/56 (9%)	2/51 (4%)	-	..
Other	10/56 (18%)	9/51 (18%)	-	..
Length of ICU stay, days	6 (4 to 13)	7 (4 to 14)	-2.0 (-3.5 to -0.6)	0.30
Length of hospital stay, days	14 (10 to 25)	16 (9 to 28)	-1.1 (-5.6 to 3.4)	0.39
Ventilator-free days at day 28, days	18 (0 to 28)	17 (0 to 28)	0.1 (-2.8 to 3.0)	0.92
Oxygenation technique-free days at day 28, days	4.5 (0 to 28)	4 (0 to 28)	0.0 (-3.1 to 3.1)	0.96
Respiratory parameters 1 h after treatment initiation				
PaO ₂ /FiO ₂ , mm Hg	143 (76)	199 (91)	-56 (-77 to -35)	<0.001
Respiratory rate, breaths per min	27 (7)	29 (8)	-1.6 (-3.4 to 0.1)	0.059
Change in discomfort scale, mm	-4 (-18 to 4)	0 (-16 to 17)	-8.5 (-16.2 to -0.8)	0.040
Time to intubation, h [n]	20 (5 to 58) [78]	29 (9 to 72) [67]	-2.3 (-23.4 to 18.8)	0.24

Underpowered trial → false neutrality risk

Target:

VT < 8 mL/kg PBW vs Observed VT $\approx$ 9.6 mL/kg

Interpretation

Hypercapnic Respiratory Failure

High-flow nasal cannula versus non-invasive ventilation for acute hypercapnic respiratory failure in adults: a systematic review and meta-analysis of randomized trials

Research Question

Component	Description
Population	Adults with acute hypercapnic respiratory failure
Intervention	High-Flow Nasal Cannula (HFNC)
Comparator	NIV
Outcomes	Mortality, Intubation, LOS, PaO2 and PaCO2

8 RCTs ; 528 patients

Study Characteristics

Study	NIV & Settings (P in cm H2O)	Comparator & Settings	Inclusion Criteria	Outcomes
Cong et al. 2019 n = 84	Full Face Mask PS/PEEP: 10/5 & titrated	HFNC 30-35L/min 37°C	AE-COPD in ICU	ABG at 12 hours and Day 5
Cortegiani et al. 2020 n = 79	Oro-nasal mask PEEP: 3-5 PS titrated to Vt 6- 8ml/kg	HFNC 60 L/min, 37°C	AE-COPD: pH 7.25 – 7.35 & pCO2 > 55mmHg ED and ICU	pCO2 at 2 hours
Doshi et al. 2020 ; n = 65	Full Face Mask CPAP PEEP: 5 -10 PS: 10-20 ; FiO2 1.0	HFNC 35L/min ; 37°C FiO2 1.0	COVID-19 + FiO2>40% + SaO2<94%	Change in PaCO2 and pH over time

Study Characteristics...

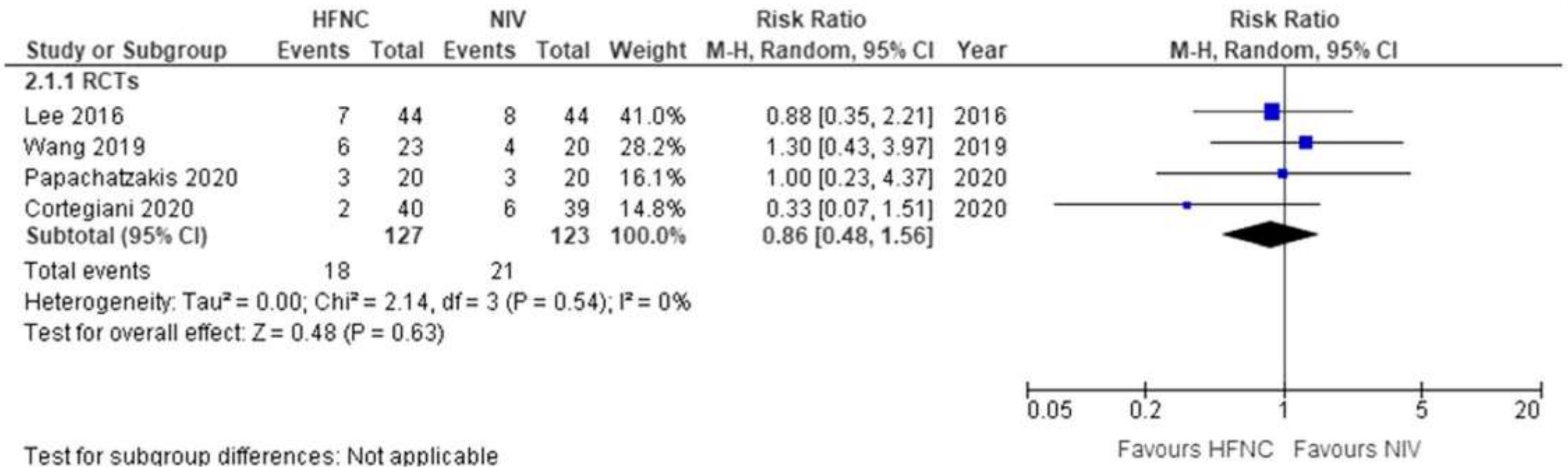
Study	NIV & Settings (P in cm H2O)	Comparator & Settings	Inclusion Criteria	Outcomes
Lee et al.2018 n = 88	Helmet NIV PS/PEEP 5/10 ; titrated to Vt 7-10 ml/kg	HFNC 35→60L/min FiO2 50% ; SpO2 92%	AE-COPD Requiring FiO2 > 50% with P/F <200, pCO2 > 45mmHg and pH 7.25 – 7.35	Intubation
Papachatzakis et al. 2020 n = 40	Full Face Mask Pressures as tolerated	HFNC 35→60L/min FiO2 50% ;SpO2 90%	ED ; T2RF with pCO2 > 45mmHg	Intubation Mortality LoS
Rezaei et al. 2020; n = 30 Cross-over RCT	Helmet NIV Settings not described	HFNC 15-35 L/min for 30 minutes ; 37°C	ED ; AE-COPD with pCO2 > 45mmHg and pH 7.25 – 7.35	Respiratory Rate Heart Rate ABG

Treatment for 30 min→1 hour washout→Switch therapy

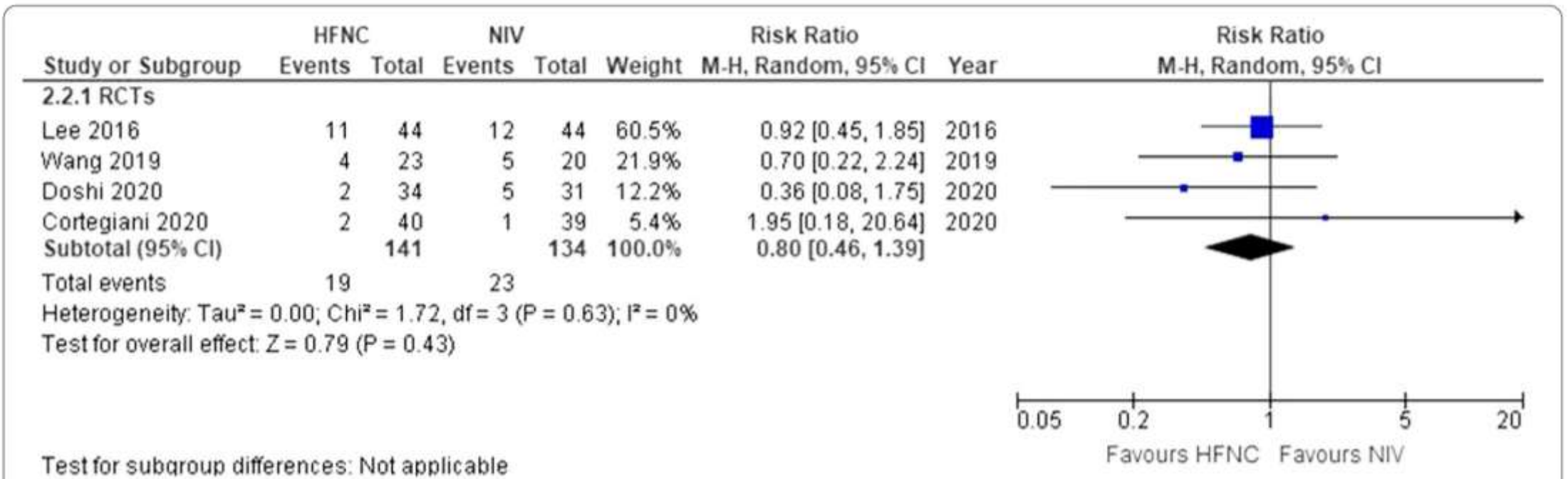
Study Characteristics...

Study	NIV & Settings (P in cm H2O)	Comparator & Settings	Inclusion Criteria	Outcomes
Sklar et al. 2018 ; n = 15	Face mask NIV Settings not Described 30 minutes	HFNC 55L/min 30 minute	Cystic Fibrosis with PaCO2 > 45mmHg	SpO2, Respiratory Rate, Comfort
Crossover after 10 minutes CoT				
Wang et al. 2019 ; n = 30	Full Face Mask Settings not Described	HFNC Settings not Described	AE-COPD	Intubation

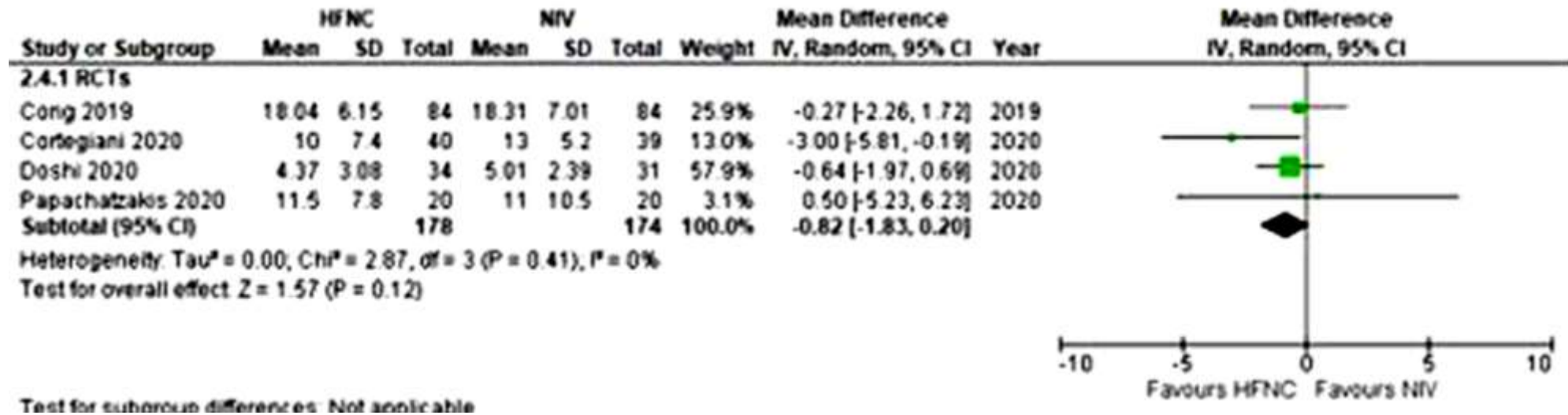
No difference in mortality



No difference in Intubation rates



Hospital Length of Stay

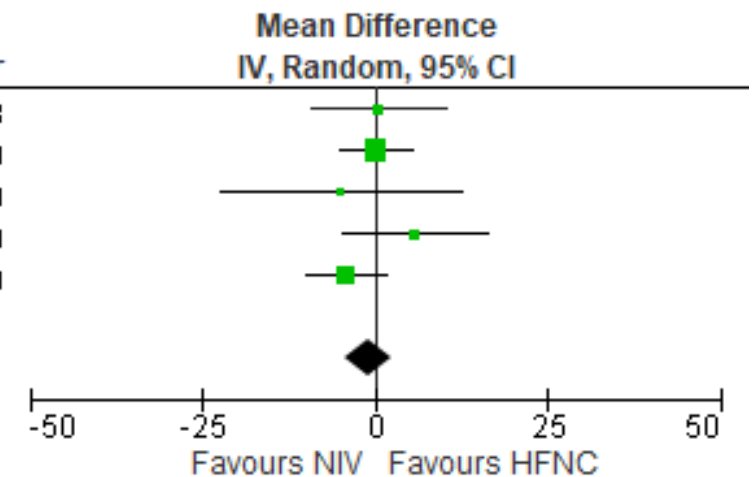


No change in PaO₂

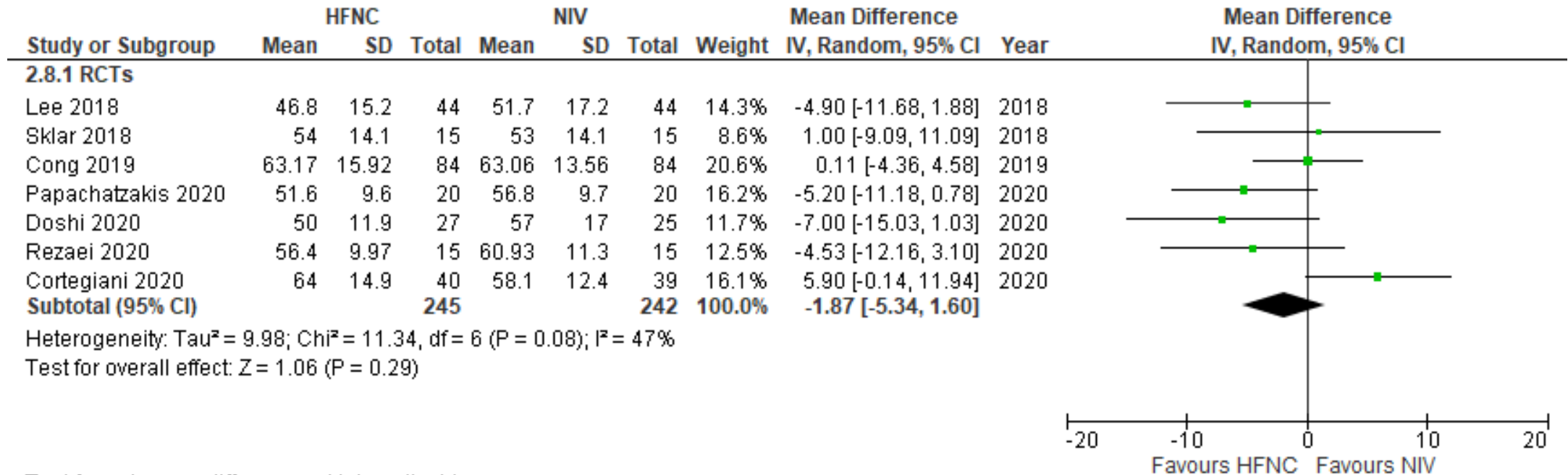
Study or Subgroup	HFNC			NIV			Weight	Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Lee 2018	82.2	24.9	44	81.6	21.7	44	12.1%	0.60 [-9.16, 10.36]	2018
Cong 2019	72.16	17.53	84	71.99	17.49	84	41.2%	0.17 [-5.13, 5.47]	2019
Doshi 2020	83	43.7	27	88	14.8	25	3.8%	-5.00 [-22.47, 12.47]	2020
Cortegiani 2020	3.1	20.7	40	-2.6	26.6	39	10.4%	5.70 [-4.83, 16.23]	2020
Papachatzakis 2020	67.9	8.8	20	72	10.4	20	32.4%	-4.10 [-10.07, 1.87]	2020
Total (95% CI)			215			212	100.0%	-0.78 [-4.18, 2.62]	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.07$, $df = 4$ ($P = 0.55$); $I^2 = 0\%$

Test for overall effect: $Z = 0.45$ ($P = 0.65$)



No change in PaCO₂



Test for subgroup differences: Not applicable

Conclusion

Intubation - No difference ; Low Certainty

Mortality - No difference ; Low Certainty

Hospital LoS - No difference ; High Certainty

Change in PaO₂ - No difference ; Low Certainty

Change in PaO₂ - No difference ; Low Certainty

High-Flow Nasal Oxygen vs Noninvasive Ventilation in Patients With Acute Respiratory Failure RENOVAE Randomized Clinical Trial

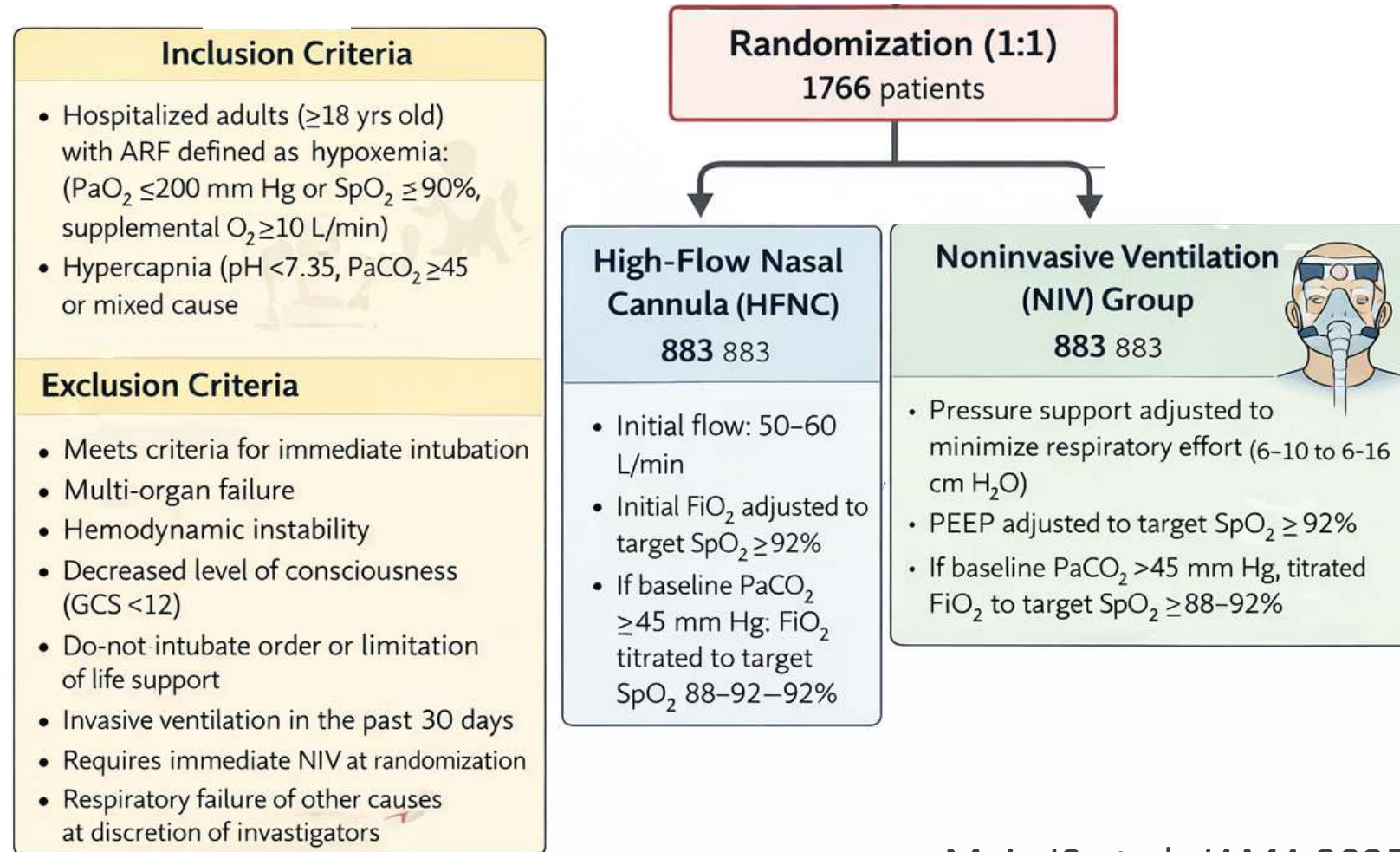
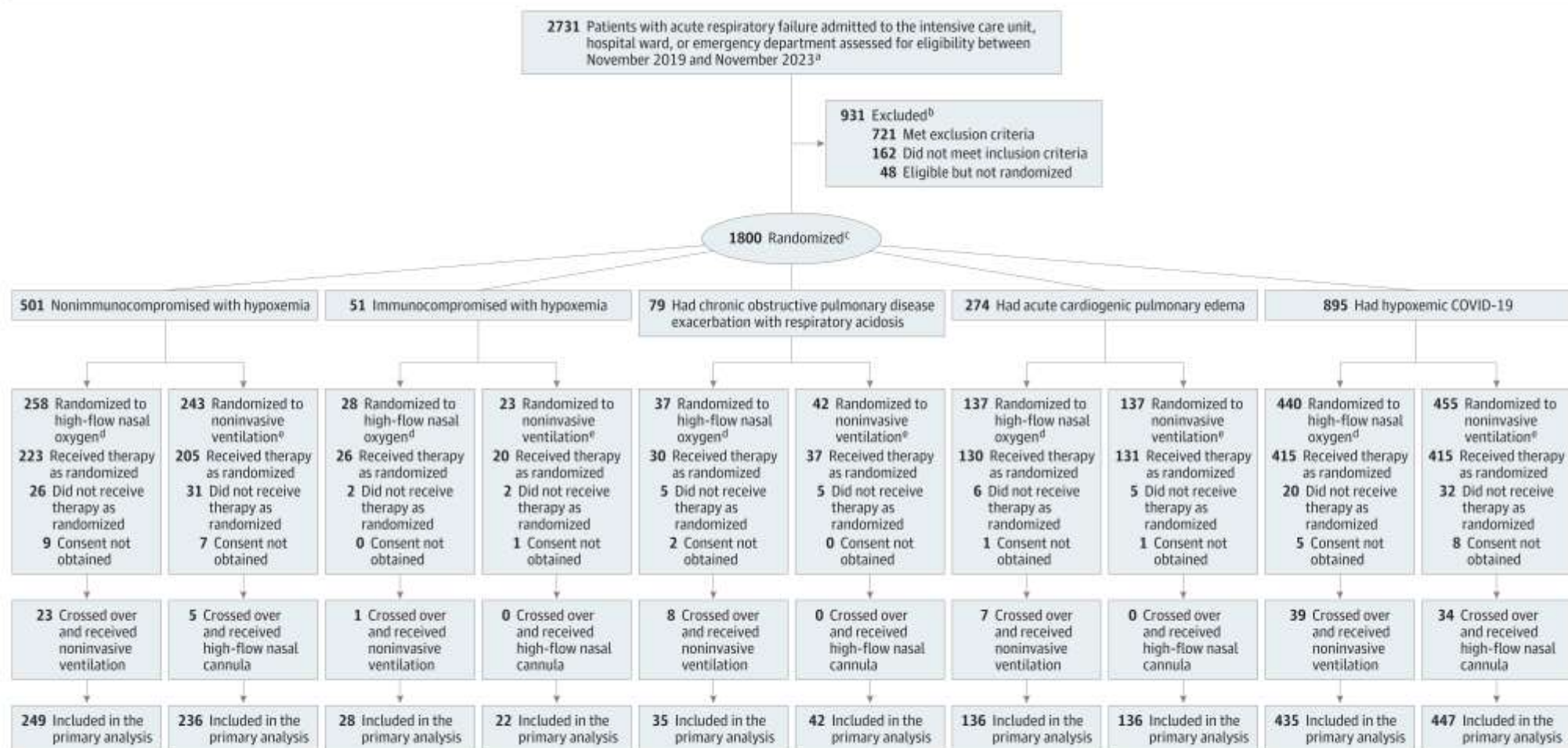


Figure 1. Enrollment, Randomization, and Follow-Up in the Study



^aInvestigators registered all patients assessed for eligibility during the trial period; however, they did not collect data on the total number of potentially eligible patients.

^bPatients may have met more than 1 reason for exclusion. Detailed counts of individual exclusions stratified by the selected patient groups with acute respiratory failure appear in the eMethods and in eFigures 2-5 in Supplement 1.

^cPatients or next of kin were asked to provide consent after randomization. The reason for postrandomization

exclusion was death before their next of kin could provide consent and lack of authorization from the ethics committee to include the data.

^dDelivered through a nasal cannula with larger-bore tubing.

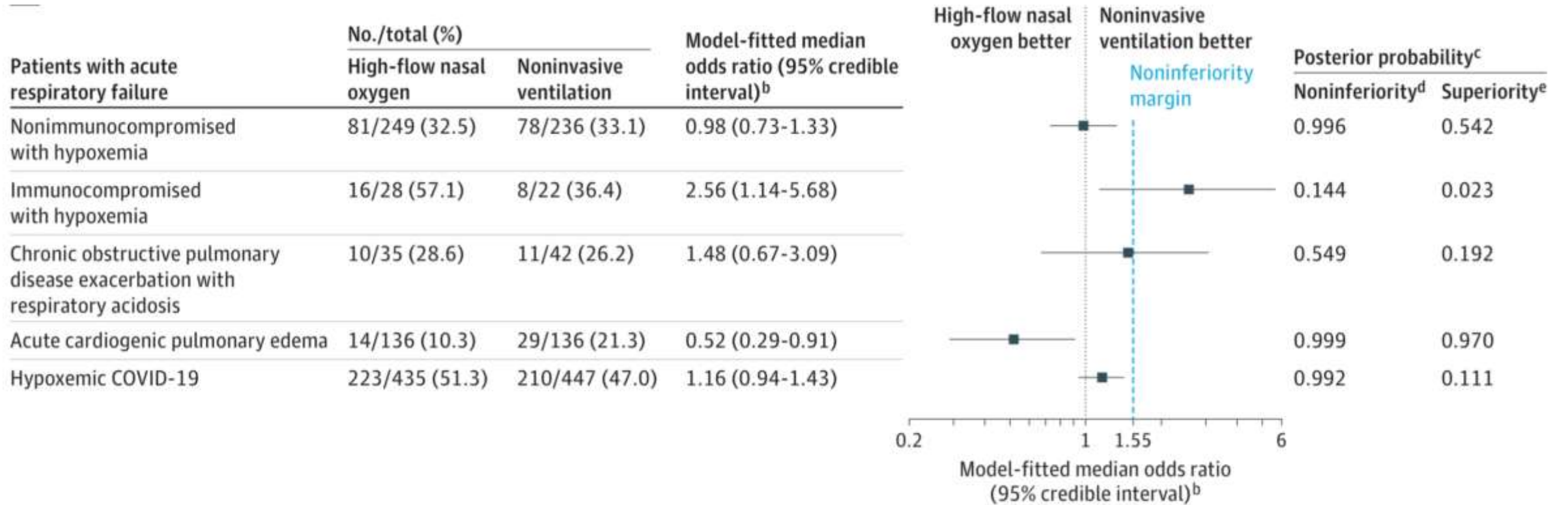
^eNoninvasive positive-pressure ventilation delivered through a face mask using either a ventilator in the intensive care unit or a bilevel device.

Results

	No. of events/total No. of patients (%)		Effect estimate (95% credible interval)		Posterior probability of superiority ^a
Patient groups with acute respiratory failure	High-flow nasal oxygen	Noninvasive ventilation	Absolute	Relative	
Nonimmunocompromised with hypoxemia					
Primary outcome of endotracheal intubation or death within 7 d	81/250 (32.4)	78/236 (33.1)	MD, 0.5 (−4.5 to 4.6)	MOR, 1.02 (0.81 to 1.26)	0.687
Individual components of primary outcome					
Endotracheal intubation within 7 d	78/250 (31.2)	69/236 (29.2)			
Death within 7 d	30/250 (12.0)	29/236 (12.3)			
Secondary outcomes ^b					
28-d mortality	61/249 (24.5)	67/236 (28.4)	MD, −1.1 (−5.5 to 2.9) ^c	MOR, 0.94 (0.74 to 1.17)	0.687
90-d mortality	74/249 (29.7)	80/236 (33.9)	MD, −4.1 (−12.3 to 3.9)	MHR, 0.86 (0.61 to 1.15)	0.826
No. of ICU-free days at 28 d, median (IQR), d [No.] ^d	19 (−1 to 24) [240]	21 (−1 to 24) [231]	MD, 0 (−2 to 2.8)	MPOR, 1.00 (0.69 to 1.34)	0.496
No. of ventilator-free days at 28 d, median (IQR), d [No.] ^d	28 (−1 to 28) [242]	28 (−1 to 28) [231]	MD, 0.9 (−2.31 to 4.1)	MPOR, 1.16 (0.8 to 1.63)	0.795
Immunocompromised with hypoxemia					
Primary outcome of endotracheal intubation or death within 7 d	16/28 (57.1)	8/22 (36.4)	MD, 1.4 (−4.9 to 7.5)	MOR, 1.07 (0.81 to 1.39)	0.526
Individual components of primary outcome					
Endotracheal intubation within 7 d	14/28 (50.0)	7/22 (31.8)			
Death within 7 d	5/28 (17.9)	3/22 (13.6)			
Secondary outcomes ^b					
28-d mortality	15/28 (53.6)	10/22 (45.5)	MD, −0.2 (−6.3 to 6.0) ^c	MOR, 0.99 (0.76 to 1.30)	0.523
90-d mortality	17/28 (60.7)	13/22 (59.1)	MD, 1.6 (24.9 to 27.1)	MHR, 1.29 (0.47 to 2.41)	0.242
No. of ICU-free days at 28 d, median (IQR), d [No.] ^d	−1 (−1 to 19) [27]	13 (−1 to 24) [22]	MD, −4.2 (−12.4 to 4.6)	MPOR, 0.48 (0.11 to 1.25)	0.102
No. of ventilator-free days at 28 d, median (IQR), d [No.] ^d	−1 (−1 to 28) [28]	26 (−1 to 28) [22]	MD, −4.0 (−13.9 to 6.2)	MPOR, 0.56 (0.11 to 1.38)	0.136
Chronic obstructive pulmonary disease exacerbation with respiratory acidosis					
Primary outcome of endotracheal intubation or death within 7 d	10/35 (28.6)	11/42 (26.2)	MD, 0.8 (−4.0 to 5.3)	MOR, 1.05 (0.79 to 1.36)	0.546
Individual components of primary outcome					
Endotracheal intubation within 7 d	10/35 (28.6)	10/42 (23.8)			
Death within 7 d	3/35 (8.6)	1/42 (2.4)			
Secondary outcomes ^b					
28-d mortality	8/35 (22.9)	8/42 (19.0)	MD, −0.2 (−4.0 to 3.7) ^c	MOR, 0.98 (0.75 to 1.29)	0.546
90-d mortality	11/35 (31.4)	13/42 (31.0)	MD, 0.5 (−20.1 to 20.8)	MHR, 1.09 (0.39 to 2.24)	0.416
No. of ICU-free days at 28 d, median (IQR), d [No.] ^d	22 (0 to 28) [33]	22 (12 to 25) [39]	MD, 0.2 (−6.6 to 7.1)	MPOR, 1.05 (0.33 to 2.23)	0.541
No. of ventilator-free days at 28 d, median (IQR), d [No.] ^d	28 (0 to 28) [33]	28 (20 to 28) [39]	MD, −1.0 (−8.4 to 6.2)	MPOR, 0.82 (0.22 to 1.93)	0.360

	No. of events/total No. of patients (%)		Effect estimate (95% credible interval)		Posterior probability of superiority ^a
Patient groups with acute respiratory failure	High-flow nasal oxygen	Noninvasive ventilation	Absolute	Relative	
Acute cardiogenic pulmonary edema					
Primary outcome of endotracheal intubation or death within 7 d	14/136 (10.3)	29/136 (21.3)	MD, -0.3 (-3.7 to 2.4)	MOR, 0.97 (0.73 to 1.23)	0.608
Individual components of primary outcome					
Endotracheal intubation within 7 d	12/136 (8.8)	27/136 (19.9)			
Death within 7 d	7/136 (5.1)	16/136 (11.8)			
Secondary outcomes ^b					
28-d mortality	19/136 (14.0)	24/136 (17.6)	MD, -0.5 (-4.0 to 3.2) ^c	MOR, 0.97 (0.74 to 1.40)	0.608
90-d mortality	23/136 (16.9)	30/136 (22.1)	MD, -5.1 (-14.7 to 4.3)	MHR, 0.73 (0.38 to 1.18)	0.872
No. of ICU-free days at 28 d, median (IQR), d [No.] ^d	28 (20 to 28) [131]	28 (17 to 28) [132]	0.7 (-2.0 to 3.3)	MPOR, 1.19 (0.68 to 1.80)	0.749
No. of ventilator-free days at 28 d, median (IQR), d [No.] ^d	28 (28 to 28) [132]	28 (26 to 28) [132]	2.2 (-0.8 to 5.5)	MPOR, 1.85 (0.95 to 3.17)	0.983
Hypoxemic COVID-19					
Primary outcome of endotracheal intubation or death within 7 d	223/435 (51.3)	210/437 (48.1)	MD, 3.1 (-1.5 to 7.9)	MOR, 1.13 (0.94 to 1.38)	0.568
Individual components of primary outcome					
Endotracheal intubation within 7 d	219/435 (50.3)	209/437 (47.8)			
Death within 7 d	34/435 (7.8)	17/437 (3.9)			
Secondary outcomes ^b					
28-d mortality	97/435 (22.3)	102/447 (22.8)	MD, -0.4 (-4.0 to 3.3) ^e	MOR, 0.98 (0.79 to 1.21)	0.568
90-d mortality	126/435 (29.0)	129/447 (28.9)	MD, 0.2 (-5.7 to 6.1)	MHR, 0.98 (0.76 to 1.25)	0.560
No. of ICU-free days at 28 d, median (IQR), d [No.] ^d	15 (0 to 21) [434]	17 (0 to 22) [439]	MD, -1.0 (-3.1 to 1.1)	MPOR, 0.85 (0.67 to 1.06)	0.840
No. of ventilator-free days at 28 d, median (IQR), d [No.] ^d	24 (1 to 28) [434]	28 (0 to 28) [441]	MD, -0.4 (-2.8 to 1.9)	MPOR, 0.94 (0.75 to 1.19)	0.310

Post-hoc analysis of Primary Outcome



Interpretation

- HFNC non-inferior – unlike FLORALI
- Robust Design
- Inferiority Margin
- Borrowing
- Heterogenous population

Post-Extubation



The efficacy of high-flow nasal cannula (HFNC) versus non-invasive ventilation (NIV) in patients at high risk of extubation failure: a systematic review and meta-analysis

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European Journal of Medical Research, 2023

Research Question

Component	Description
Population	Adults at high risk of extubation failure
Intervention	High-Flow Nasal Cannula (HFNC)
Comparator	NIV
Outcomes	Re-Intubation, Mortality, LOS

PRISMA FLOWCHART

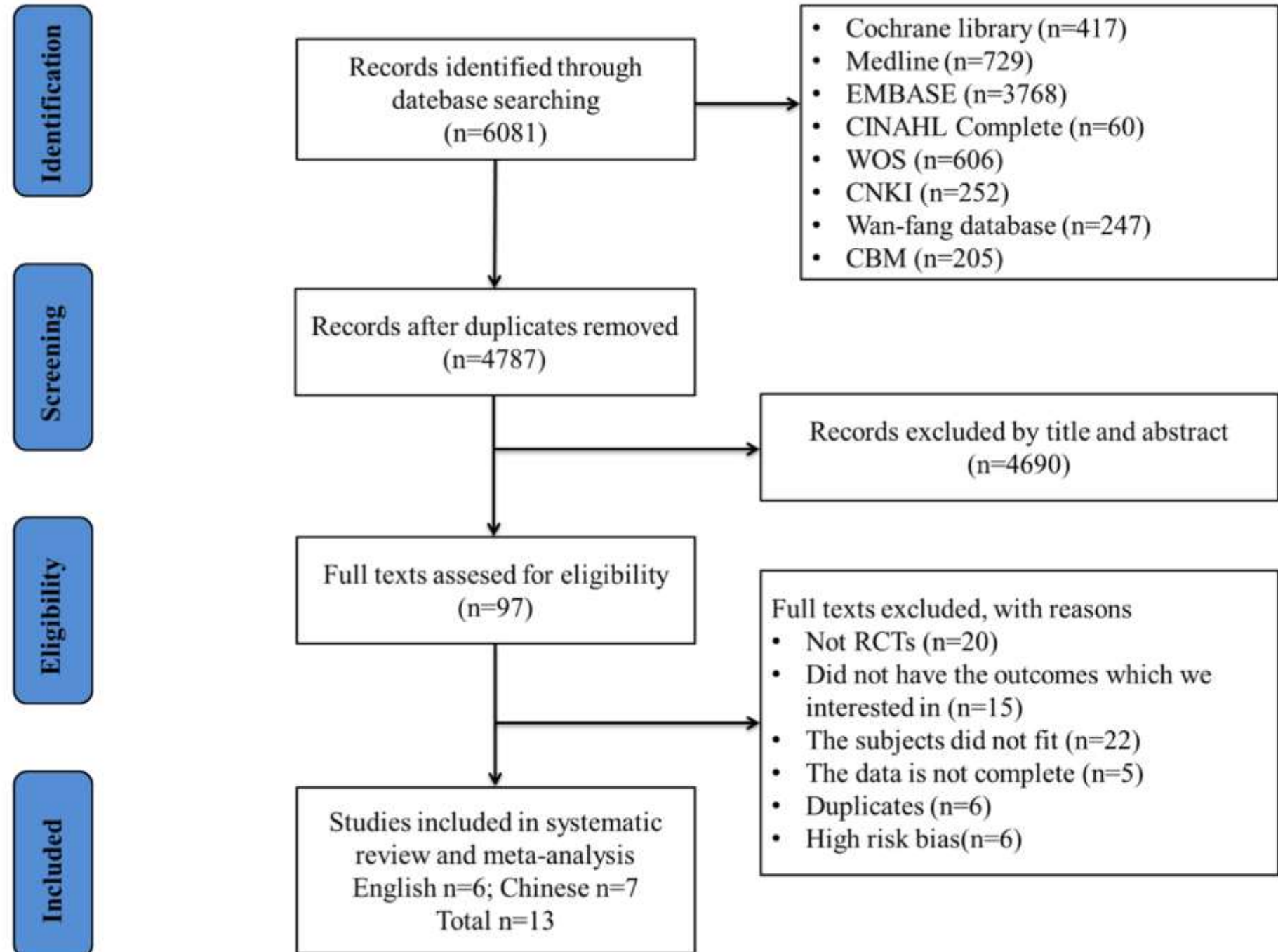


Table 1 Basic characteristics of the study were included

Study	Year	Region	Disease	Sample(n)		Sex (male/female)		Age ($\bar{x} \pm s$, years)		Intervention		Grade (risk of bias)	Included outcomes
				HFNC	NIV	HFNC	NIV	HFNC	NIV	HFNC	NIV		
Hernández et al	2016	France	High-risk patients	290	314	186/104	202/112	64.6 $\pm$ 15.4	64.4 $\pm$ 15.8	37°C, 10L/min, 5L/min was increased until the patient felt unwell	IPAP and EPAP were adjusted to target a Rr of 25/ min and adequate gas exchange	A	(1)(2)(3)(4)(5)(6)
Hu et al	2018	China	AECOPD	60	60	34/26	30/30	NA	NA	37°C, 40L/min, keep SpO ₂ > 92%	IPAP 10–12 cm H ₂ O, EPAP 4–6 cmH ₂ O	B	(1)(4)(5)(7)
Jiang et al	2019	China	AECOPD	18	17	13/5	11/6	75.0 $\pm$ 5.1	71.0 $\pm$ 6.5	50L/min, keep SpO ₂ > 92%	5–8cmH ₂ O EPAP, keep SpO ₂ > 92%	B	(1)(3)(4)(5)(7)
Jing et al	2019	China	COPD	22	20	NA	NA	77.4 $\pm$ 6.8	73.9 $\pm$ 6.9	37°C, keep SpO ₂ 88%–92%	IPAP 10–12 cmH ₂ O, EPAP 4–5cmH ₂ O	A	(1)(2)(3)(4)(5)(6)(7)
Liu et al	2019	China	COPD	44	43	24/20	22/21	64.1 $\pm$ 10.5	65.1 $\pm$ 9.7	20–40 L/min	IPAP 4 cmH ₂ O, 5–10 min increased 2 cmH ₂ O, keep 8–20cmH ₂ O, EPAP 4–6cmH ₂ O	B	(1)(2)(5)(7)
Shang et al	2021	China	APACHEII > 12	24	24	12/12	13/11	66.92 $\pm$ 4.58	67.7 $\pm$ 6.89	37°C, 40L/min, keep SpO ₂ > 90%	10–12cmH ₂ O IPAP, 4–6cmH ₂ O EPAP	B	(1)(2)(3)(4)(5)(7)
Tan et al	2020	China	COPD	44	42	27/17	24/19	68.4 $\pm$ 9.3	71.4 $\pm$ 7.8	37°C, 50L/min, keep SpO ₂ 88%–92%	8cmH ₂ O IPAP, 4cmH ₂ O EPAP	A	(1)(2)(3)(4)(5)(6)(7)
Tongyoo et al	2021	Thai-land	> 65	60	58	NA	NA	> 65	> 65	37°C, 30L/min, 10 min increased 5L/min until 50L/min	8cmH ₂ O IPAP, 5cmH ₂ O EPAP, IPAP increased 2cmH ₂ O per 10 min	A	(1)
Wang et al	2021	China	SAP with ARDS	30	30	25/5	24/6	43 $\pm$ 7	41 $\pm$ 7	37°C, 40–50L/min, keep SpO ₂ > 95%	IPAP 5–12cmH ₂ O, EPAP 0–5cmH ₂ O	B	(1)(2)(3)(4)(5)(6)(7)

Table 1 (continued)

Study	Year	Region	Disease	Sample(n)		Sex (male/female)		Age ($\bar{x} \pm s$, years)		Intervention		Grade (risk of bias)	Included outcomes
				HFNC	NIV	HFNC	NIV	HFNC	NIV	HFNC	NIV		
Xu et al	2021	China	COPD	50	50	32/18	30/20	69.2 $\pm$ 6.13	68.3 $\pm$ 5.22	37°C, FiO ₂ 30%–50%, 50 L/min, keep SpO ₂ 88%–92%	EPAP 4–5mmH ₂ O, IPAP 10–12mmH ₂ O, keep SpO ₂ 88%–92%	B	(1)(4)
Yang et al	2015	China	Post- cardiac surgery	20	20	14/6	13/2	53.8 $\pm$ 8.9	52.9 $\pm$ 7.8	37°C, 45 L/min	IPAP 10–12cmH ₂ O, EPAP 4–6 cmH ₂ O	B	(1)(2)(3)(4)(5)(6)(7)
Yu et al	2019	China	COPD	36	36	24/12	21/15	62.4 $\pm$ 10.1	63.5 $\pm$ 11.2	37°C, 30–60 L/min, FiO ₂ 30%–80%	IPAP 10–14 cmH ₂ O, EPAP 4–6 cmH ₂ O	B	(1)(2)(4)(5)(6)(7)
Zhang et al	2018	China	COPD	21	24	18/3	20/4	64.5 $\pm$ 5.3	66.1 $\pm$ 6.6	37°C, 40L/min, when SpO ₂ = 92%, change 30L/min	IPAP 5–15 cmH ₂ O, EPAP 0–5cmH ₂ O	B	(1)(2)(3)(4)(5)(6)

HFNC: high-flow nasal cannula oxygen therapy, NIV: non-invasive ventilation, AECOPD: acute exacerbation of chronic obstructive pulmonary disease, COPD: chronic obstructive pulmonary disease, SAP: severe acute pancreatitis, ARDS: acute respiratory distress syndrome, IPAP: inspiratory positive airway pressure, EPAP: expiratory positive airway pressure, Reintubation rates

(1) Reintubation rates

(2) Mortality rate

(3) ICU length of stay

(4) Incidence of adverse events

(5) Partial pressure of carbon dioxide

(6) Oxygenation index

(7) Respiratory rate

Re-Intubation

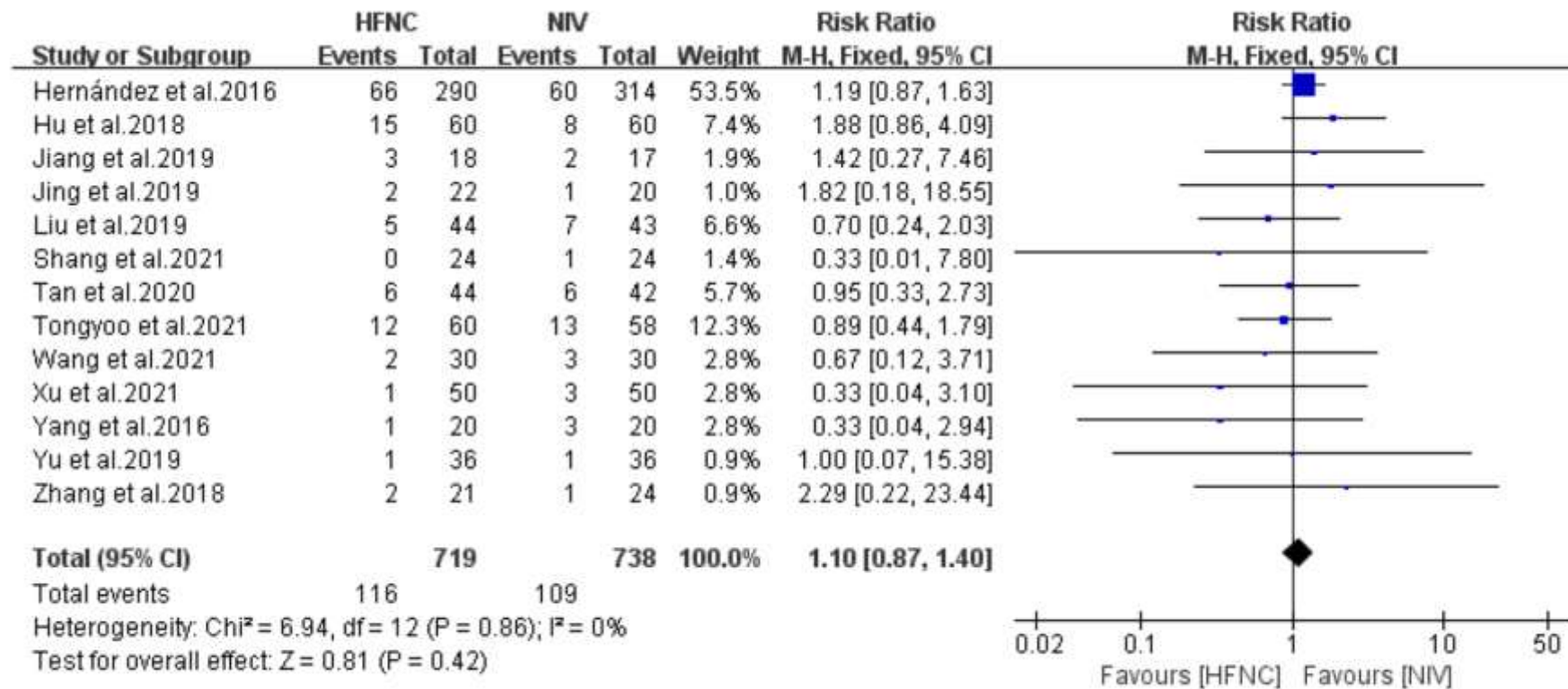


Fig. 4 Forest plots for reintubation between high-flow nasal cannula and non-invasive ventilation

Mortality

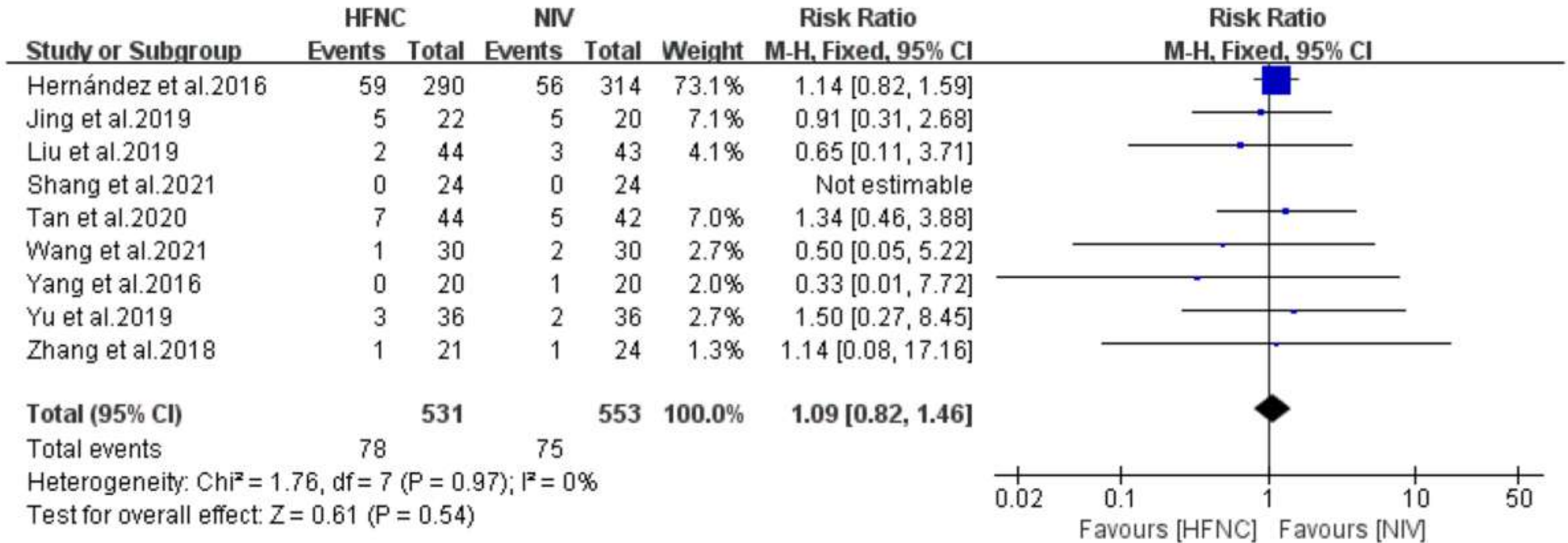


Fig. 5 Forest plots for mortality between high-flow nasal cannula and non-invasive ventilation

ICU Length of Stay

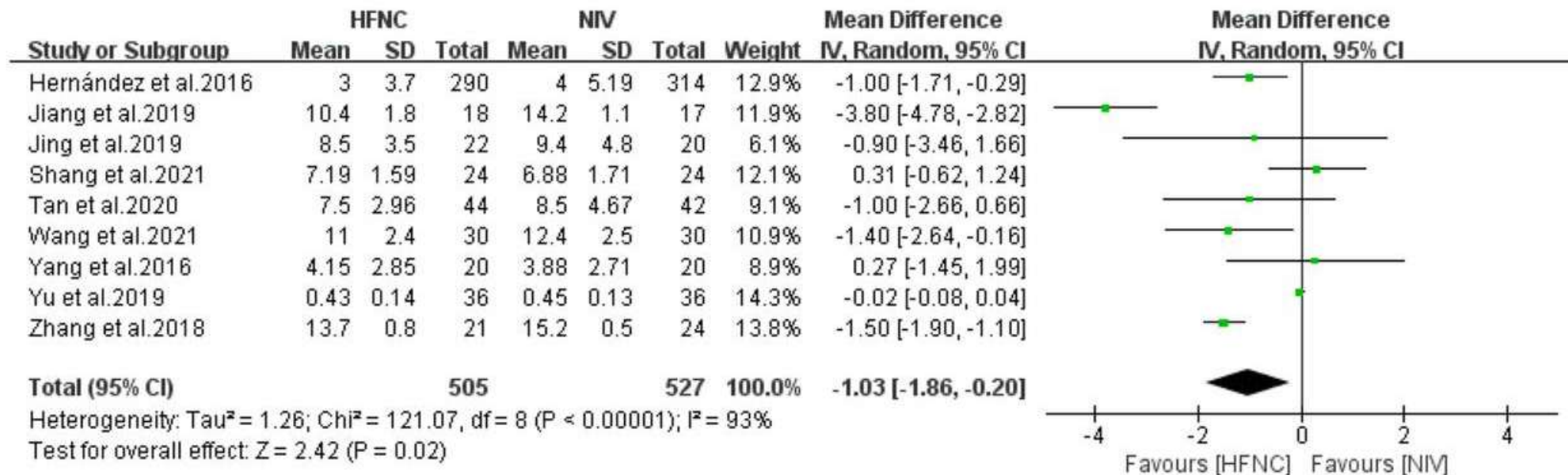


Fig. 6 Length of ICU stay forest plot between high-flow nasal cannula and non-invasive ventilation

Length of Stay

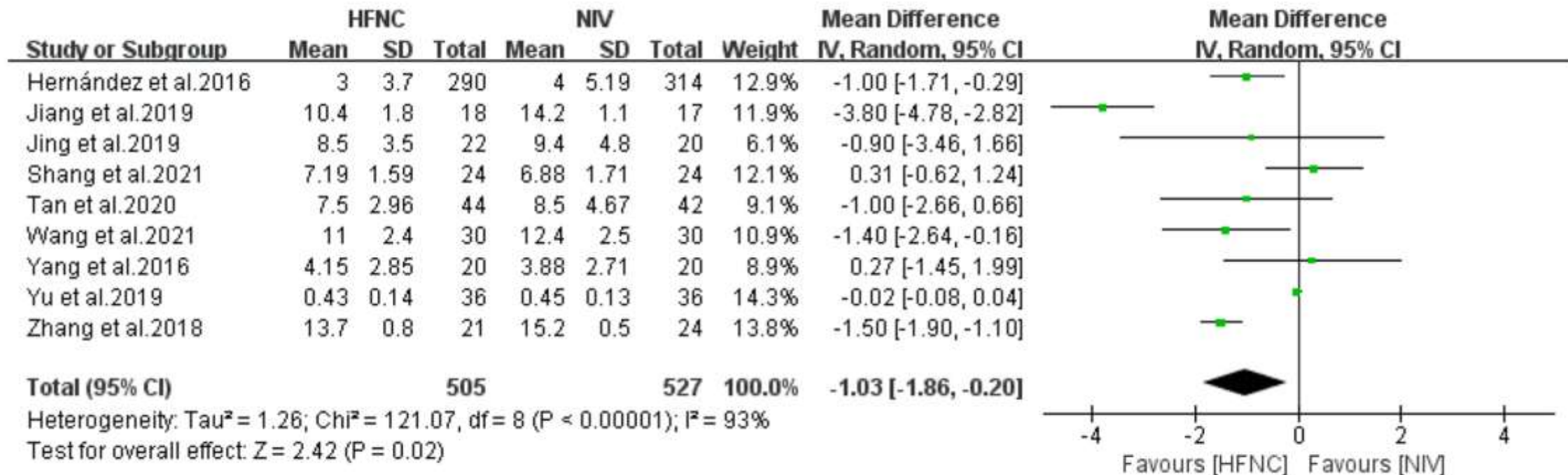
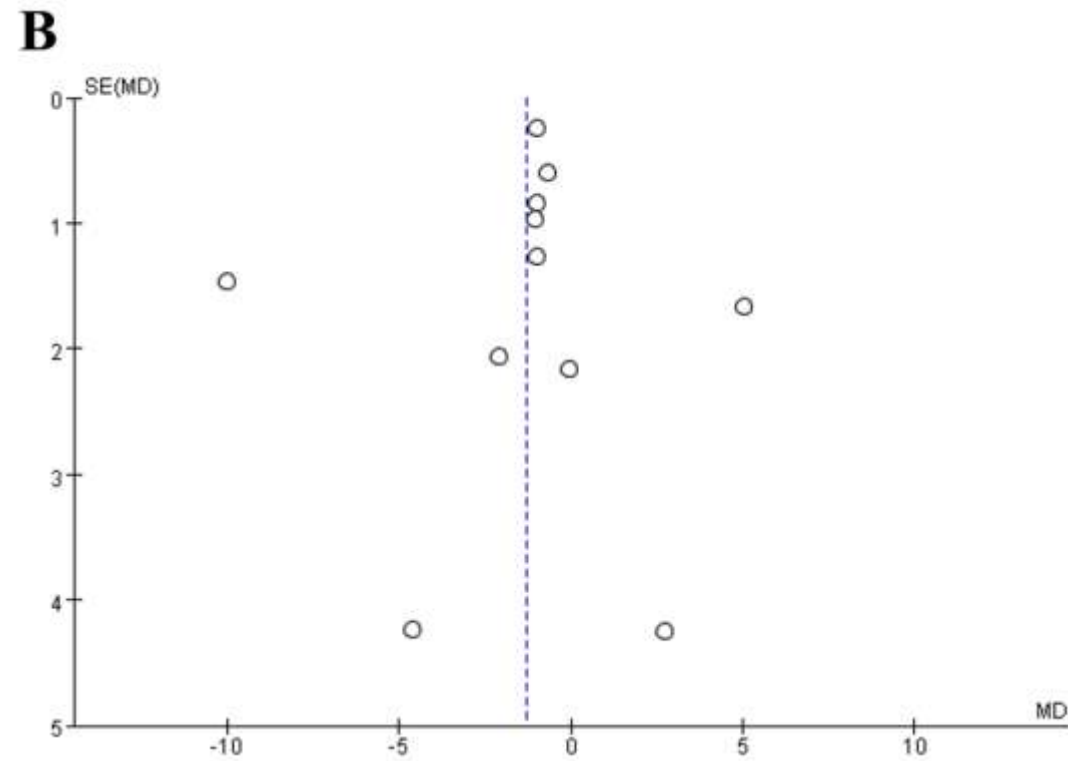


Fig. 6 Length of ICU stay forest plot between high-flow nasal cannula and non-invasive ventilation

Interpretation

- Publication bias
- Heterogeneity



Effect of Post-extubation High-Flow Nasal Cannula vs Non-invasive Ventilation on Reintubation and Post-extubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial

Population:

- IMV > 12 hours and ready for extubation

Exclusion criteria

- DNR orders
- Tracheostomies
- Hypercapnia during SBT
- Accidental extubation, or self-extubation.

At-least one risk factor for reintubation:

- Age > 65 years
- heart failure as the primary indication for mechanical ventilation
- moderate-to-severe COPD
- APACHE II > 12 points on day of extubation
- BMI > 30
- absence of airway patency problem
- >2 comorbidities
- IMV > 7 days

.

Intervention

HFNC Group

- applied immediately after extubation
- Flow started at 10 L/min and increased by 5-L/min steps until patients experienced discomfort
- FIO₂ titrated to target SpO₂ > 92%
- After 24 hours, high-flow therapy was stopped and, if necessary, patients received conventional oxygen therapy.

NIV Group

- Full face mask NIV immediately after extubation for 24 hours
- Afterwards, NIV was withdrawn and oxygen was administered by Venturi mask
- PEEP and PS adjusted to RR > 25/min with pH of 7.35
- FiO₂ titrated to SpO₂ > 92%
- Sedatives to increase tolerance to NIV were not allowed.

RESULTS

Table 2. Primary and Secondary Outcomes

	No. (%)		
	Noninvasive Mechanical Ventilation (n = 314)	High-Flow Conditioned Oxygen Therapy (n = 290)	Difference Between Groups (95% CI) ^a
Primary outcome			
All-cause reintubation ^b	60 (19.1)	66 (22.8)	-3.7 (-9.1 to ∞) ^c
Postextubation respiratory failure ^b	125 (39.8)	78 (26.9)	12.9 (6.6 to ∞) ^c
Secondary Outcomes			
Causes of postextubation respiratory failure			<i>P</i> = .89 ^d
Respiratory acidosis ^e	21 (6.7)	11 (3.8)	
Hypoxia ^f	19 (6.1)	12 (4.1)	
Unbearable dyspnea	26 (8.3)	21 (7.2)	
Decreased level of consciousness	7 (2.2)	4 (1.4)	
Inability to clear secretions	52 (16.6)	30 (10.3)	
Causes for reintubation			<i>P</i> = .28 ^d
Cardiorespiratory arrest	3 (1)	3 (1)	
Agitation	1 (0.3)	3 (1)	
Inability to clear secretions	20 (6.4)	13 (4.5)	
Hemodynamic impairment ^g	10 (3.2)	14 (4.8)	
Persistent postextubation respiratory failure ^f	16 (5.1)	16 (5.5)	
Nonrespiratory causes for reintubation			
Surgery	4 (1.3)	2 (0.7)	
Low level of consciousness ^h	6 (1.9)	15 (5.2)	
Adverse eventsⁱ	135 (42.9)	0 (0)	<i>P</i> < .001
Sepsis	4 (1.3)	6 (2.1)	-0.8 (-3.3 to 1.5) ^{d,j}
Multiorgan failure	5 (1.6)	5 (1.7)	-0.1 (-2.6 to 2.2) ^{d,j}
Respiratory infection	34 (10.8)	23 (7.9)	2.9 (-1.8 to 7.6) ^j
Ventilator-associated tracheobronchitis	18 (5.7)	11 (3.8)	1.9 (-1.6 to 5.5) ^j
Ventilator-associated pneumonia	17 (5.4)	12 (4.1)	1.3 (-2.3 to 4.8) ^j
Time to reintubation, median (IQR), h	21.5 (10 to 47)	26.5 (14 to 39)	-5 (-34 to 24) ^{j,k}
ICU length of stay, median (IQR), d	4 (2 to 9)	3 (2 to 7)	1 (-0.1 to 2.1) ^{k,l}
Hospital length of stay, median (IQR), d	26 (16 to 37)	23 (14 to 46)	3 (-6.8 to -0.8) ^{k,l}
Mortality			
ICU	18 (5.7)	19 (6.6)	-0.8 (-4.9 to 3.1) ^j
Hospital	56 (17.8)	59 (20.3)	-2.5 (-8.8 to 3.8) ^{d,j}

INTERPRETATION

Duration of Therapy

- Reintubations mostly happened after 24 hours

Heterogeneous “High-Risk” Population

- Cannot generalize results

Summary

Likely similar outcomes across groups – Intubation, Mortality

Choice:

T1RF – Either Device

T2RF – NIV > HFNC

Immunocompromised – Either Device

Post Extubation – Either Device