UPDATES IN MANAGEMENT OF ARDS

Dr Akshay Raut

1. Definition
2. Phenotypes

Respiratory management of ARDS

1. HFNO
2. NIV
3. Tidal Volume
4. PEEP
5. Recruitment Manoeuvres
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7. NMB
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ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies

2023

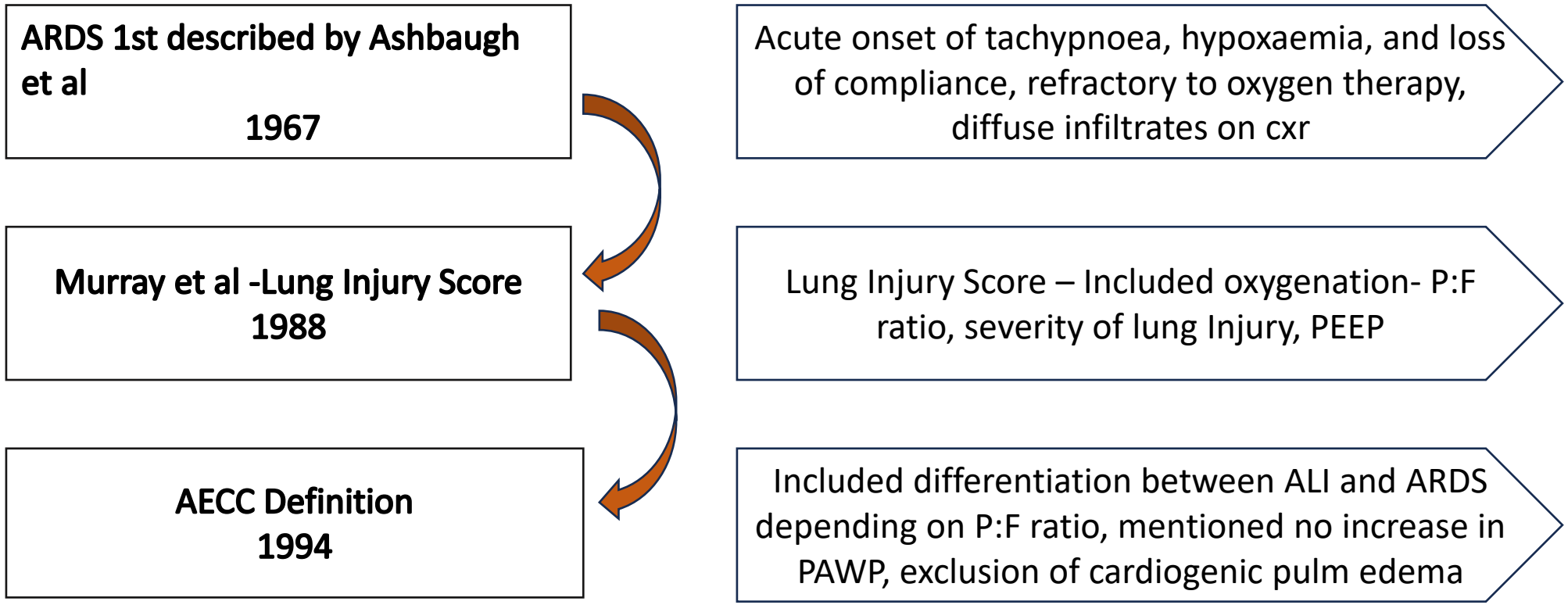
AMERICAN THORACIC SOCIETY DOCUMENTS

An Update on Management of Adult Patients with Acute Respiratory Distress Syndrome

An Official American Thoracic Society Clinical Practice Guideline

2024

Definition of ARDS

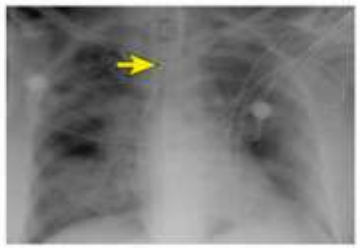
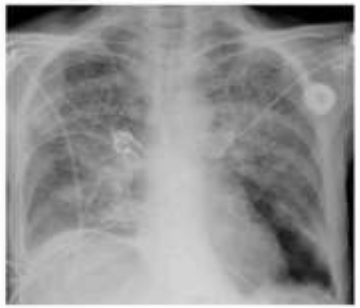
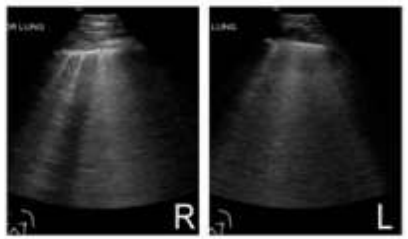


Berlin Definition
2012

Future Definition

Berlin Definition	Rationale for Updating Criteria	How This is Addressed in the Global Definition
Acute onset within 1 week of known insult or new or worsening respiratory symptoms	Onset may be more indolent for some insults, such as COVID-19	The inclusion of patients with HFNO will capture patients with more indolent courses, and therefore the timing criterion has not been changed
Bilateral opacities on chest radiography or computed tomography not fully explained by effusions, lobar/lung collapse, or nodules	Chest radiography and computed tomography not available in some clinical settings	Ultrasound can be used to identify bilateral loss of lung aeration (multiple B lines and/or consolidations) as long as operator is well trained in the use of ultrasound
Three severity categories defined by Pa_{O_2}:$F_{I_{O_2}}$	Pulse oximetric measurement of Sp_{O_2}:$F_{I_{O_2}}$ is widely used and validated as a surrogate for Pa_{O_2}:$F_{I_{O_2}}$	Sp_{O_2}:$F_{I_{O_2}}$ can be used for diagnosis and assessment of severity if Sp_{O_2} is ≤97%
Requirement for invasive or noninvasive mechanical ventilation such that PEEP ≥ 5 cm H_2O is required for all categories of oxygenation severity except mild, which can also be met with CPAP ≥ 5 cm H_2O	HFNO increasingly being used in patients with severe hypoxemia who otherwise meet ARDS criteria Invasive and noninvasive mechanical ventilation not available in resource-limited settings	New category of nonintubated ARDS created for patients on HFNO at ≥30 L/min who otherwise meet ARDS criteria Modified definition of ARDS for resource-limited settings does not require Pa_{O_2}:$F_{I_{O_2}}$, PEEP, or HFNO

(Matthay et al., New Global Definition of ARDS.,ATS Journals,2024)

Patient Description		Imaging	Oxygenation	ARDS Categories
	68-year-old M with abdominal sepsis, septic shock, and acute hypoxemic respiratory failure		Mechanically ventilated FiO_2 0.5 PaO_2 75 P/F = 150 mm Hg	**Intubated ARDS** Severity: Moderate *Typical patient included in prior Berlin definition*
	54-year-old F with history of breast cancer, COVID-19 pneumonia, and worsening shortness of breath for the past 6 days		High-flow nasal oxygen HFNO 40L/min FiO_2 0.80 SpO_2 91% S/F = 114	**Nonintubated ARDS** *New category in Global definition*
	39-year-old F with abdominal sepsis and gram-negative bacteremia in a small under-resourced hospital without blood gases, radiography, or mechanical ventilation		Supplemental oxygen by face mask at 15L/min FiO_2 0.6 SpO_2 85% S/F = 142	**ARDS in resource-limited settings** *New category in global definition, consistent with the Kigali modification*

(Matthay et al., New Global Definition of ARDS.,ATS Journals,2024)

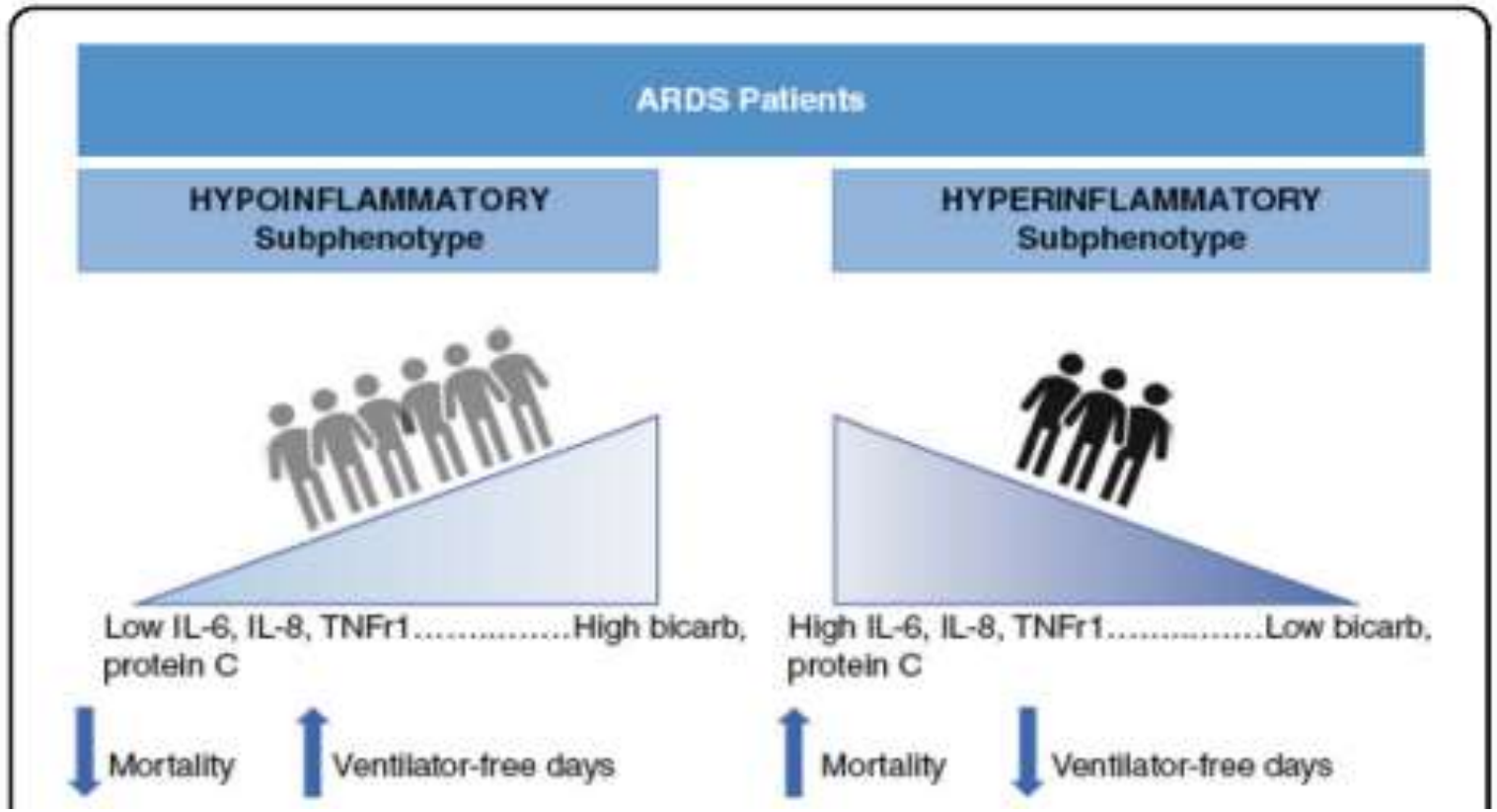
	Criteria That Apply to All ARDS Categories		
Risk factors and origin of edema	Precipitated by an acute predisposing risk factor, such as pneumonia, nonpulmonary infection, trauma, transfusion, aspiration, or shock. Pulmonary edema is not *exclusively or primarily* attributable to cardiogenic pulmonary edema/fluid overload, and hypoxemia/gas exchange abnormalities are not primarily attributable to atelectasis. However, ARDS can be diagnosed in the presence of these conditions if a predisposing risk factor for ARDS is also present.		
Timing	Acute onset or worsening of hypoxemic respiratory failure within 1 week of the estimated onset of the predisposing risk factor or new or worsening respiratory symptoms.		
Chest imaging	Bilateral opacities on chest radiography and computed tomography or bilateral B lines and/or consolidations on ultrasound* not fully explained by effusions, atelectasis, or nodules/masses.		
	Criteria That Apply to Specific ARDS Categories		
	Nonintubated ARDS†	**Intubated ARDS**	**Modified Definition for Resource-Limited Settings‡**
Oxygenation§‖	$Pa_{O_2}:FI_{O_2} \leq 300$ mm Hg or $Sp_{O_2}:FI_{O_2} \leq 315$ (if $Sp_{O_2} \leq 97\%$) on HFNO with flow of ≥30 L/min or NIV/CPAP with at least 5 cm H_2O end-expiratory pressure	Mild¶: $200 < Pa_{O_2}:FI_{O_2} \leq 300$ mm Hg or $235 < Sp_{O_2}:FI_{O_2} \leq 315$ (if $Sp_{O_2} \leq 97\%$) Moderate: $100 < Pa_{O_2}:FI_{O_2} \leq 200$ mm Hg or $148 < Sp_{O_2}:FI_{O_2} \leq 235$ (if $Sp_{O_2} \leq 97\%$) Severe: $Pa_{O_2}:FI_{O_2} \leq 100$ mm Hg or $Sp_{O_2}:FI_{O_2} \leq 148$ (if $Sp_{O_2} \leq 97\%$)	$Sp_{O_2}:FI_{O_2} \leq 315$ (if $Sp_{O_2} \leq 97\%$)†. Neither positive end-expiratory pressure nor a minimum flow rate of oxygen is required for diagnosis in resource-limited settings.

(Matthay et al., New Global Definition of ARDS.,ATS Journals,2024)

ARDS Phenotyping

- **Phenotype** - A clinically observable set of traits resulting from an interaction of genotype and environmental exposures (i.e., ARDS is a phenotype)
- **Subgroup -** A subset of patients within a phenotype, which may be defined using any cut-off in a variable (e.g., PaO2/FiO2 severity classification of ARDS)
- **Sub-phenotype -** A distinct subgroup (of ARDS patients) that can be reliably discriminated from other subgroups based on a set or pattern of observable or measurable properties (e.g. radiological , biological subphenotypes)
- **Endotype** – A sub-phenotype with a distinct functional or pathobiological mechanism, which preferably responds differently to a targeted therapy

new ESICM guidelines on ARDS. ESICM 2023



Calfie et al 2020

Table 3 Subphenotype-specific treatment response in the reanalyses of outcomes in four different clinical ARDS trials

Intervention/trial cohort analyzed		Hypoinflammatory subphenotype response		Hyperinflammatory subphenotype response	
	Outcome	Intervention	Control	Intervention	Control
High vs. low PEEP/ ALVEOLI* [27]	90-day mortality	24% high PEEP	16% low PEEP	42% high PEEP	51% low PEEP
Conservative vs. liberal fluid strategy/ FACCT* [29]	90-day mortality	18% conservative fluid strategy	26% liberal fluid strategy	50% conservative fluid strategy	40% liberal fluid strategy
Simvastatin/ HARP-2 [40]	28-day survival	No difference		Improved survival with simvastatin (p = 0.008)	
Rosuvastatin/SAILS [41]	90-day mortality	No difference		No difference	

PEEP positive end-expiratory pressure; *p value <0.05 for interaction between treatment and subphenotype

Calfie et al 2020

Respiratory Management of ARDS

1. HFNO

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

- Multicentre, open label, randomized, controlled trial
- N=310 (AHRF with P:F ≤ 300)
    - High-flow oxygen therapy (n=106)
    - Standard oxygen therapy (n=94)
    - Non-invasive ventilation (n=110)
- Included patients with AHRF with RR ≥ 25, $PaO_2:FiO_2$ ratio ≤ 300, $PaCO_2$ ≤ 45 and no clinical h/o chronic respiratory failure
- Primary outcome: Proportion of patients intubated at day 28

Frat, J.-P. et al. (2015) “High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure,” NEJM, 372(23), pp. 2185–2196

Primary Outcome				
Measure	**High-flow (n=106)**	**NIV (n=110)**	**Facemask (n=94)**	**p**
Intubation				
Intubation by day 28 – n (%)	40 (38%)	55 (50%)	44 (47%)	0.18

High flow = High flow oxygen group (also known as 'high-flow nasal cannula' or 'HFNC'); NIV = Non-invasive ventilation; n = number; % = percentage

Secondary Outcomes				
Measure	**High-flow**	**NIV**	**Facemask**	**p**
Mortality				
ICU Mortality – n (%)	10 (12%)	23 (28.4%)	16 (21.6%)	0.03
Mortality at 90 days – n (%)	11 (13%)	26 (32%)	20 (27%)	0.01
LOS ICU (assessed at 90 days)				
LOS ICU for survivors - mean days (SD)	10 (+/- 14.9)	12.4 (+/- 13.1)	8.3 (+/- 6.9)	0.96
LOS ICU for non survivors - mean days (SD)	15.9 (+/- 14.4)	14.9 (+/-13.2)	18.1 (+/- 14.8)	
Complications during ICU Stay				
Cardiac dysrhythmia – n (%)	11 (10.4%)	17 (15.4%)	16 (17.0%)	0.35
Septic shock – n (%)	19 (17.9%)	34 (30.9%)	26 (27.7%)	0.08
Cardio-respiratory arrest – n (%)	5 (4.7%)	6 (5.4%)	7 (7.4%)	0.7
Nosocomial pneumonia – n (%)	3 (3.6%)	7 (8.6%)	4 (5.4%)	0.81
Reasons for intubation				
Respiratory failure – n (%)	29 (70.7%)	43 (71.7%)	34 (75.5%)	0.41
Circulatory failure – n (%)	5 (12.1%)	5 (8.3%)	3 (6.7%)	0.6
Neurologic failure – n (%)	7 (17.1%)	12 (20%)	8 (17.8%)	0.96
Grade of dyspnoea after 1 hr of treatment				
				<0.001
Marked improvement – n (%)	19 (22.1%)	13 (4.3%)	5 (6.8%)	
Slight improvement – n (%)	46 (53.5%)	40 (44.0%)	26 (35.1%)	
No change – n (%)	18 (20.9%)	23 (25.5%)	33(44.6%)	
Slight deterioration – n (%)	3 (3.5%)	8 (8.8%)	9 (12.2%)	
Marked deterioration – n (%)	0 (0%)	7 (7.7%)	1 (1.3%)	
Respiratory patient - discomfort at inclusion - mm (SD)	38 +/-31	46 +/-30	44 +/-29	0.2
Respiratory patient - discomfort at 1hr of treatment - mm (SD)	29 +/-26	43+/-29	40+/-29	<0.01
Other				
Ventilator free days at day 28 - mean (SD)	24 (+/-8)	19 (+/-12)	22 (+/-19)	<0.02

LOS = Length of stay; SD = standard deviation

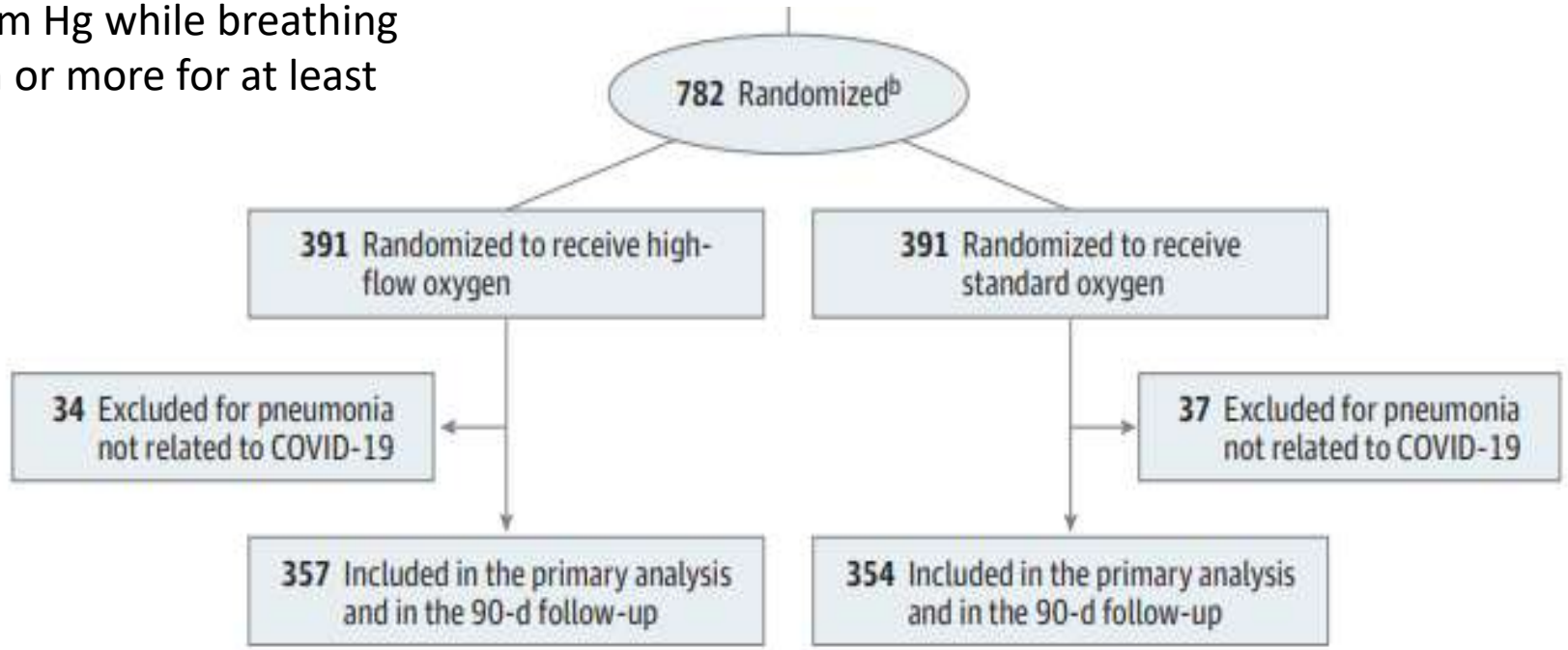
Frat, J.-P. et al. (2015) "High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure,NEJM, 372(23)

JAMA | Original Investigation

Effect of High-Flow Nasal Cannula Oxygen vs Standard Oxygen Therapy on Mortality in Patients With Respiratory Failure Due to COVID-19

The SOHO-COVID Randomized Clinical Trial

PaO2:FIO2 ≤ 200 mm Hg while breathing oxygen at 10 L/min or more for at least 15 minutes



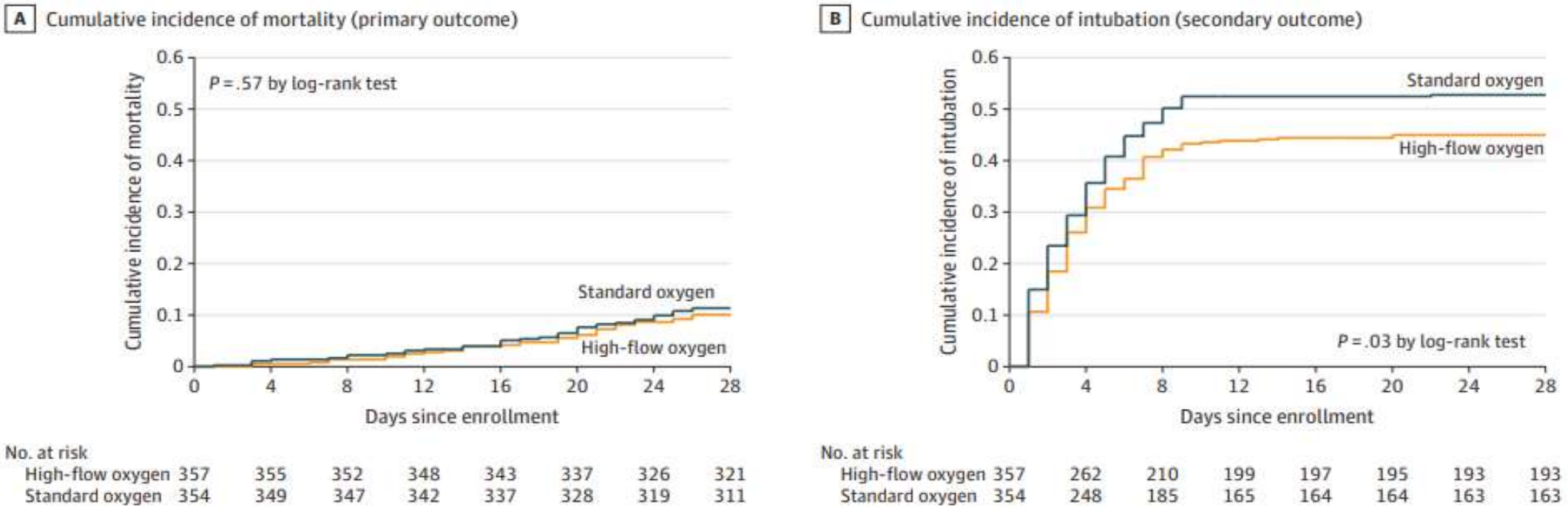
Frat, J.-P. et al. (2022) " The SOHO-COVID randomized clinical trial," JAMA: t 328(12), p. 1212. doi: 10.1001/jama.2022.15613

Table 2. Primary and Secondary Outcomes

Outcomes	High-flow oxygen (n = 357)	Standard oxygen (n = 354)	Absolute difference (95%CI)	Unadjusted odds ratio (95%CI)	*P* value for unadjusted odds ratio	Adjusted odds ratio[a,b] (95% CI)	*P* value for adjusted odds ratio
Primary outcome							
Mortality at day 28, No. (%)	36 (10)	40 (11)	-1.2 (-5.8 to 3.4)	0.88 (0.55 to 1.42)	.60	0.78 (0.48 to 1.28)	.32
Secondary outcomes							
Intubation at day 28, No. (%)	160 (45)	186 (53)	-7.7 (-14.9 to -0.4)	0.73 (0.55 to 0.99)	.04	0.65 (0.48 to 0.89)	.007
ICU mortality, No. (%)	42 (12)	52 (15)	-2.9 (-7.9 to 2.1)	0.77 (0.50 to 1.20)	.25	0.68 (0.42 to 1.05)	.08
Hospital mortality, No. (%)	46 (13)	53 (15)	-2.1 (-7.2 to 3.0)	0.84 (0.55 to 1.29)	.42	0.74 (0.48 to 1.15)	.18
Mortality at day 90, No. (%)	48 (13)	53 (15)	-1.5 (-6.7 to 3.6)	0.88 (0.58 to 1.34)	.56	0.79 (0.51 to 1.23)	.30
Ventilator-free days at day 28 median (IQR), d[c,d]	28 (11 to 28)	23 (10 to 28)	0.5 (-7.7 to 9.1)[b]		.07		

Frat, J.-P. et al. (2022) " The SOHO-COVID randomized clinical trial," JAMA: t 328(12), p. 1212. doi: 10.1001/jama.2022.15613

Figure 2. Kaplan-Meier Plot of the Cumulative Incidence of Mortality (Primary Outcome) and Intubation (Secondary Outcome) From Randomization to Day 28



The median observation time was 28 days (IQR, 28-28) in all treatment groups.

Frat, J.-P. et al. (2022) " The SOHO-COVID randomized clinical trial," JAMA: t 328(12), p. 1212. doi: 10.1001/jama.2022.15613

Role of HFNC

- To be used instead of COT – can lower the need for intubation
- Need data to suggest mortality benefit

ESICM Guidelines on ARDS

- Recommendation – Non MV patients with AHRF not due to cardiogenic pulmonary edema or AECOPD receive HFNO compare to COT **
- Unable to make recommendation for or against HFNO or COT to reduce mortality
- This recommendations applies to AHRF from COVID 19 *

new ESICM guidelines on ARDS. ESICM 2023

2. NIV

A concern regarding the use of CPAP/NIV is the potential delay in intubation, which might lead to worse outcomes, including increased mortality

Moreover, high transpulmonary pressures can be observed during NIV potentially leading to P-SILI, analogous to the VILI lung injury

In the LUNG SAFE study NIV was used in 15 % of ARDS patients, NIV use was associated with increased mortality, especially in patients with P/F <150 – 36% vs 25% (p=0.03)

new ESICM guidelines on ARDS. ESICM 2023

Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial

- The objective was to determine whether either CPAP or HFNO, compared with COT, improves clinical outcomes in COVID-19–related AHRF
- N = 1273, CPAP (n = 380), HFNO (n = 418), or COT (n = 475)
- Included covid 19 patients with AHRF – with clinical status – Fio2 ≥40%, spo2 ≤94%
- The primary outcome was a composite of tracheal intubation or mortality within 30 days

Table 3. Primary and Secondary Outcomes in the Continuous Positive Airway Pressure Group vs the Conventional Oxygen Therapy Group

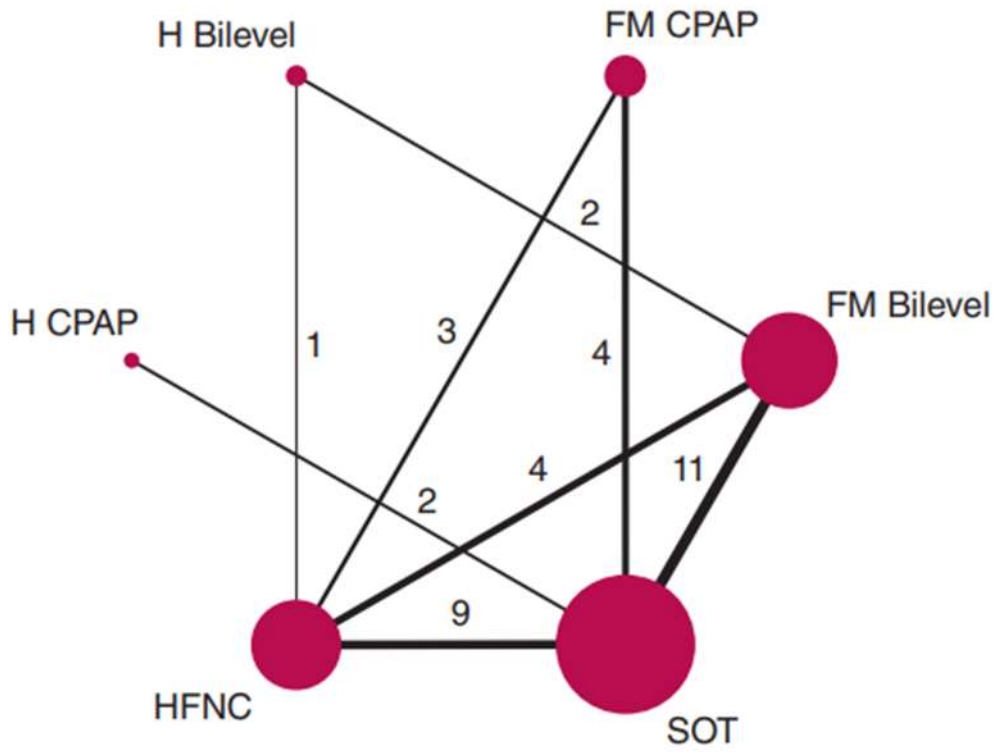
	Continuous positive airway pressure	Conventional oxygen therapy	Difference (95% CI)[a]	Unadjusted		Adjusted	
				Effect estimate (95% CI)	*P* value[b]	Effect estimate (95% CI)[c]	*P* value[b]
Primary composite outcome							
Tracheal intubation or mortality within 30 d, No./total (%)	137/377 (36.3)	158/356 (44.4)	AD, −8 (−15 to −1)	OR, 0.72 (0.53 to 0.96)	.03	OR, 0.68 (0.48 to 0.94)	.02
Secondary outcomes							
Individual components of the primary composite outcome, No./total (%)							
Tracheal intubation within 30 d	126/377 (33.4)	147/356 (41.3)	AD, −8 (−15 to −1)	OR, 0.71 (0.53 to 0.96)	.03	OR, 0.67 (0.48 to 0.93)	.02
Mortality within 30 d	63/378 (16.7)	69/359 (19.2)	AD, −3 (−8 to 3)	OR, 0.84 (0.58 to 1.23)	.37	OR, 0.91 (0.59 to 1.39)	.65
Tracheal intubation rate, No./total (%)[d]	126/377 (33.4)	147/356 (41.3)	AD, −8 (−15 to −1)	OR, 0.71 (0.53 to 0.96)	.03	OR, 0.67 (0.48 to 0.93)	.02
Admission to intensive care unit, No./total (%)	204/368 (55.4)	219/348 (62.9)	AD, −7 (−15 to −3)	OR, 0.73 (0.54 to 0.99)	.04	OR, 0.69 (0.49 to 0.96)	.03
Duration of invasive mechanical ventilation after tracheal intubation, median (IQR), d[e]	(n = 126) 15.0 (8.0 to 25.0)	(n = 147) 11.0 (6.0 to 23.0)	MDND, 4.0 (0.04 to 8.0)	HR, 0.82 (0.61 to 1.09)	.17	HR, 0.83 (0.61 to 1.12)	.22
Time to event, median (IQR), d							
Tracheal intubation[f]	(n = 126) 2.0 (1.0 to 4.0)	(n = 147) 1.0 (0 to 4.0)	MDND, 1.0 (0.2 to 1.8)	HR, 0.77 (0.61 to 0.98)	.03	HR, 0.71 (0.56 to 0.91)	.01
Death[g]	(n = 74) 17.0 (11.0 to 26.0)	(n = 79) 17.0 (11.0 to 24.0)	MDND, 0 (−3.8 to 3.8)	HR, 0.86 (0.61 to 1.21)	.38	HR, 0.93 (0.65 to 1.33)	.69
Mortality, No./total (%)							
During intensive care unit stay	62/204 (30.4)	66/219 (30.1)	AD, 3 (−9 to 9)	OR, 1.01 (0.67 to 1.53)	.95	OR, 1.10 (0.69 to 1.75)	.68
During hospital stay	72/364 (19.8)	78/346 (22.5)	AD, −3 (−9 to 3)	OR, 0.85 (0.59 to 1.22)	.37	OR, 0.92 (0.62 to 1.38)	.69
Length of stay, mean (SD), d							
Intensive care unit[h]	(n = 368) 9.5 (15.6)	(n = 348) 9.6 (13.6)	MD, −0.08 (−2.23 to 2.07)		.94	MD, −0.16 (−2.30 to 1.99)	.88
Hospital[i]	(n = 364) 16.4 (17.5)	(n = 346) 17.3 (18.1)	MD, −0.96 (−3.59 to 1.67)		.47	MD, −1.14 (−3.84 to 1.55)	.41

Table 4. Primary and Secondary Outcomes in the High-Flow Nasal Oxygen Group vs the Conventional Oxygen Therapy Group

	High-flow nasal oxygen	Conventional oxygen therapy	Difference (95% CI)[a]	Unadjusted		Adjusted	
				Effect estimate (95% CI)	*P* value[b]	Effect estimate (95% CI)[c]	*P* value[b]
Primary composite outcome							
Tracheal intubation or mortality within 30 d, No./total (%)	184/415 (44.3)	166/368 (45.1)	AD, −1 (−8 to 6)	OR, 0.97 (0.73 to 1.29)	.83	OR, 0.94 (0.68 to 1.29)	.69
Secondary outcomes							
Individual components of the primary composite outcome, No./total (%)							
Tracheal intubation within 30 d	170/415 (41.0)	153/368 (41.6)	AD, −1 (−8 to 6)	OR, 0.98 (0.73 to 1.30)	.86	OR, 0.94 (0.69 to 1.30)	.72
Mortality within 30 d	78/416 (18.8)	74/370 (20.0)	AD, −1 (−7 to 4)	OR, 0.92 (0.65 to 1.32)	.66	OR, 0.97 (0.65 to 1.46)	.90
Tracheal intubation rate, No./total (%)[d]	169/415 (40.7)	154/368 (41.8)	AD, −1 (−8 to 6)	OR, 0.95 (0.72 to 1.27)	.75	OR, 0.92 (0.67 to 1.27)	.62
Admission to intensive care unit, No./total (%)	252/408 (61.8)	214/361 (59.3)	AD, 2 (−4 to 9)	OR, 1.11 (0.83 to 1.48)	.48	OR, 1.04 (0.75 to 1.45)	.81
Duration of invasive mechanical ventilation after tracheal intubation, median (IQR), d[e]	(n = 169) 15.0 (8.0 to 26.0)	(n = 154) 12.0 (6.0 to 23.0)	MDND, 3.0 (−1.0 to 7.0)	HR, 0.92 (0.71 to 1.20)	.56	HR, 1.01 (0.76 to 1.34)	.96
Time to event, median (IQR), d							
Tracheal intubation[f]	(n = 169) 1.0 (0 to 3.0)	(n = 154) 1.0 (0 to 3.0)	MDND, 0 (−0.4 to 0.4)	HR, 0.98 (0.78 to 1.21)	.82	HR, 0.92 (0.74 to 1.16)	.49
Death[g]	(n = 88) 16.5 (9.0 to 22.5)	(n = 85) 17.0 (11.0 to 24.0)	MDND, 0 (−3.4 to 3.4)	HR, 0.94 (0.68 to 1.29)	.69	HR, 0.94 (0.67 to 1.32)	.74
Mortality, No./total (%)							
During intensive care unit stay	72/251 (28.7)	65/214 (30.4)	AD, −2 (−10 to 7)	OR, 0.92 (0.62 to 1.38)	.69	OR, 0.98 (0.63 to 1.54)	.94
During hospital stay	86/405 (21.2)	80/359 (22.3)	AD, −1 (−7 to 5)	OR, 0.94 (0.67 to 1.33)	.73	OR, 0.99 (0.67 to 1.47)	.97
Length of stay, mean (SD), d							
Intensive care unit[h]	(n = 407) 10.5 (15.6)	(n = 361) 9.6 (14.1)	MD, 0.95 (−1.16 to 3.07)		.38	MD, 0.47 (−1.57 to 2.50)	.65
Hospital[i]	(n = 405) 18.3 (20.0)	(n = 359) 17.1 (18.0)	MD, 1.21 (−1.50 to 3.93)		.38	MD, 0.33 (−2.28 to 2.94)	.80

Noninvasive oxygen strategies in adult patients with AHRF : A systematic review and meta-analysis (oct 2023)

- 36 trials – 7046 patients - incorporated evidence from COVID 19 trials also

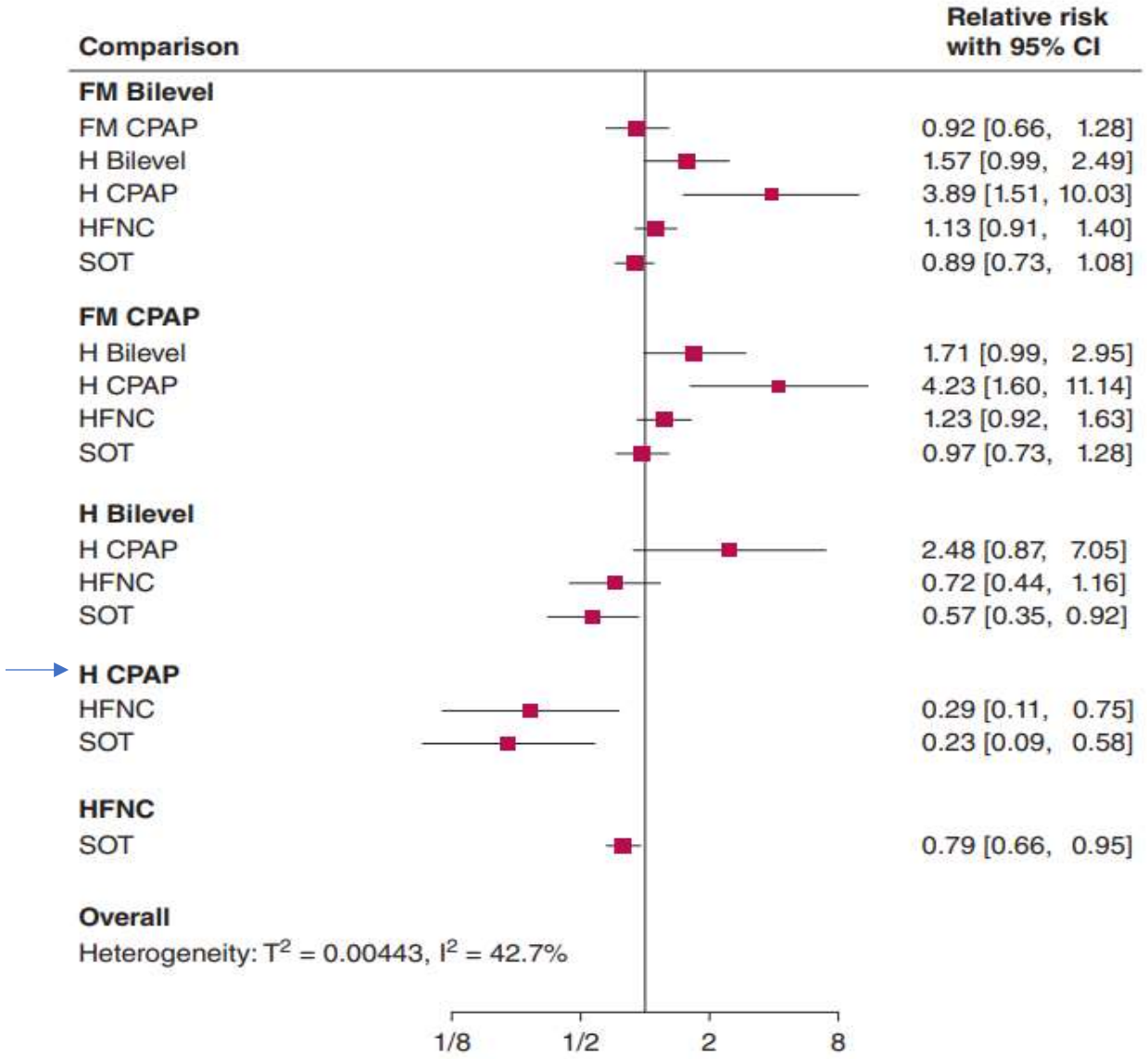


Tyler Pitre et al Chest Journals 2023

- Helmet CPAP probably reduces mortality compared with standard oxygen therapy (SOT) (231 fewer deaths per 1,000; 95% CI, 126-273 fewer)
- HFNC probably reduces the need for invasive mechanical ventilation(103.5 fewer events per 1,000; 95% CI, 40.5-157.5 fewer)
- All noninvasive oxygenation strategies may reduce the duration of hospitalization as compared with SOT (low certainty)
- Helmet bilevel ventilation (4.84 days fewer) and helmet CPAP (1.74 days fewer) may reduce the duration of ICU stay as compared with SOT

	Benefit Outcomes [Risk difference per 1,000 (95% CI)]		Efficacy Outcomes [Mean Difference (95% CI)]		
Oxygen Strategy	**Death**	**IMV**	**Duration of Hospitalization**	**Duration of ICU**	**Ventilator-Free Days**
Standard oxygen therapy	300 per 1,000	450 per 1,000	...	...	...
HFNC	−63 (−102 to −15)[a,b]	−103.5 (−157.5 to −40.5)[a]	−1.35 (−2.42 to −0.28)[a,c]	−0.88 (−1.92 to 0.16)[a,b]	2.53 (−0.08 to 5.15)[a,c]
H CPAP	−231 (−273 to −126)[a]	−306 (−373.5 to −189)[a,d]	−1.42 (−3.77 to 0.93)[a,c]	−1.74 (−4.49 to 1.01)[a,c]	
H bilevel	−129 (−195 to −24)[a,d]	−351 (−400.5 to −256.5)[a,d]	−6.17 (−10.72 to −1.63[a,b]	−4.84 (−7.36 to −2.33)[a,d]	8.51 (2.96 to 14.07)[a,c]
FM bilevel	−36 (−84 to 24)[a,b]	−99 (−157.5 to −27)[a]	−1.07 (−2.60 to 0.66)[a,c]	−0.42 (−1.56 to 0.73)[a,c]	−0.82 (−4.53 to 2.9)[a,c]
FM CPAP	−9 (−81 to 84)[a,c]	−76.5 (−166.5 to 36)[a,e]	−1.00 (−2.62 to 0.66)[a,c]	−0.68 (−2.3 to 0.94)[a,c]	1.33 (−3.55 to 6.21)[a,c]

Tyler Pitre et al Chest Journals 2023



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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

- Patients with mod to severe hypoxemic RF due to covid 19 (P:F <200)
- N = 109
- CPAP with helmet NIV (PEEP/PS – 10-12 cm H2o) for atleast 48 hrs
- Primary outcome - number of days free of respiratory support within 28 days after enrollment in Helmet vs HFNC (20 vs 18)
- The rate of ET intubation was significantly lower in the helmet group

  30% vs 51% (P= 0.03)
- Median number of days free of invasive MV within 28 days was significantly higher in the helmet group – 28 vs 25 (0.04)
- Hospital mortality - similar

- Role of NIV in ARDS – non-COVID-19 – still controversial
- Helmet CPAP – showed promising results
- No mortality benefit

ESICM Guidelines on ARDS 2023

- CPAP/NIV can be considered instead of HFNO for the treatment of AHRF due to COVID-19 to reduce the risk of intubation – weak recommendation
- No recommendation can be made for whether CPAP/NIV can decrease mortality compared to HFNO in COVID-19

3. **Tidal volume**

Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome

- 2 groups -> Vt - 12 ml/kg PBW, plateu pressure ≤ 50

  Vt – 6 ml/kg PBW, plateu pressure ≤ 30

- First primary outcome was death before a patient was discharged home and was breathing without assistance
- Second primary outcome was the number of days without ventilator use from day 1 to day 28
- 861 patients

Ventilation with lower tidal volumes compared to traditional tidal volumes for acute lung injury and acute respiratory distress syndrome. (2000). *NEJM*, *342*(18), 1301–1308.

- Mortality was lower in lower Vt than in the group treated with traditional Vt (31.0 percent vs. 39.8 percent, P=0.007)
- The number of days without ventilator use during the first 28 days was greater in lower Vt group (P=0.007)

Recommendation

- It is recommended to use low tidal volume ventilation strategies (i.e., 4–8 ml/kg PBW), compared to larger tidal volumes to reduce mortality in patients with ARDS***
- It also applies to COVID 19

4 & 5 - PEEP and recruitment manoeuvres

- **Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome**
- 549 patients with acute lung injury and ARDS
- Receive MV with either lower or higher PEEP levels
- Predetermined combinations of PEEP and fio2

Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. (2004). NEJM, 351(4)

Allowable combinations of PEEP and FiO_2†														
Lower-PEEP group														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
Higher-PEEP group (before protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22–24	
Higher-PEEP group (after protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0				
PEEP	12	14	14	16	16	18	20	22	22	22–24				

Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. (2004). NEJM, 351(4)

- The rates of death before hospital discharge were 24.9 percent and 27.5, lower peep vs higher peep respectively (P=0.48)
- From day 1 to day 28, breathing was unassisted for a mean of 14.5±10.4 days in the lower-PEEP group and 13.8±10.6 days in the higher-PEEP group (P=0.50)

Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. (2004). NEJM, 351(4)

Recommendations ESICM

We are **unable to make a recommendation** for or against routine PEEP titration with a higher PEEP/FiO_2 strategy versus a lower PEEP/FiO_2 strategy to reduce mortality in patients with ARDS.
No recommendation; high level of evidence of no effect.

This statement applies also to ARDS from COVID-19.
No recommendation; moderate level of evidence of no effect for indirectness.

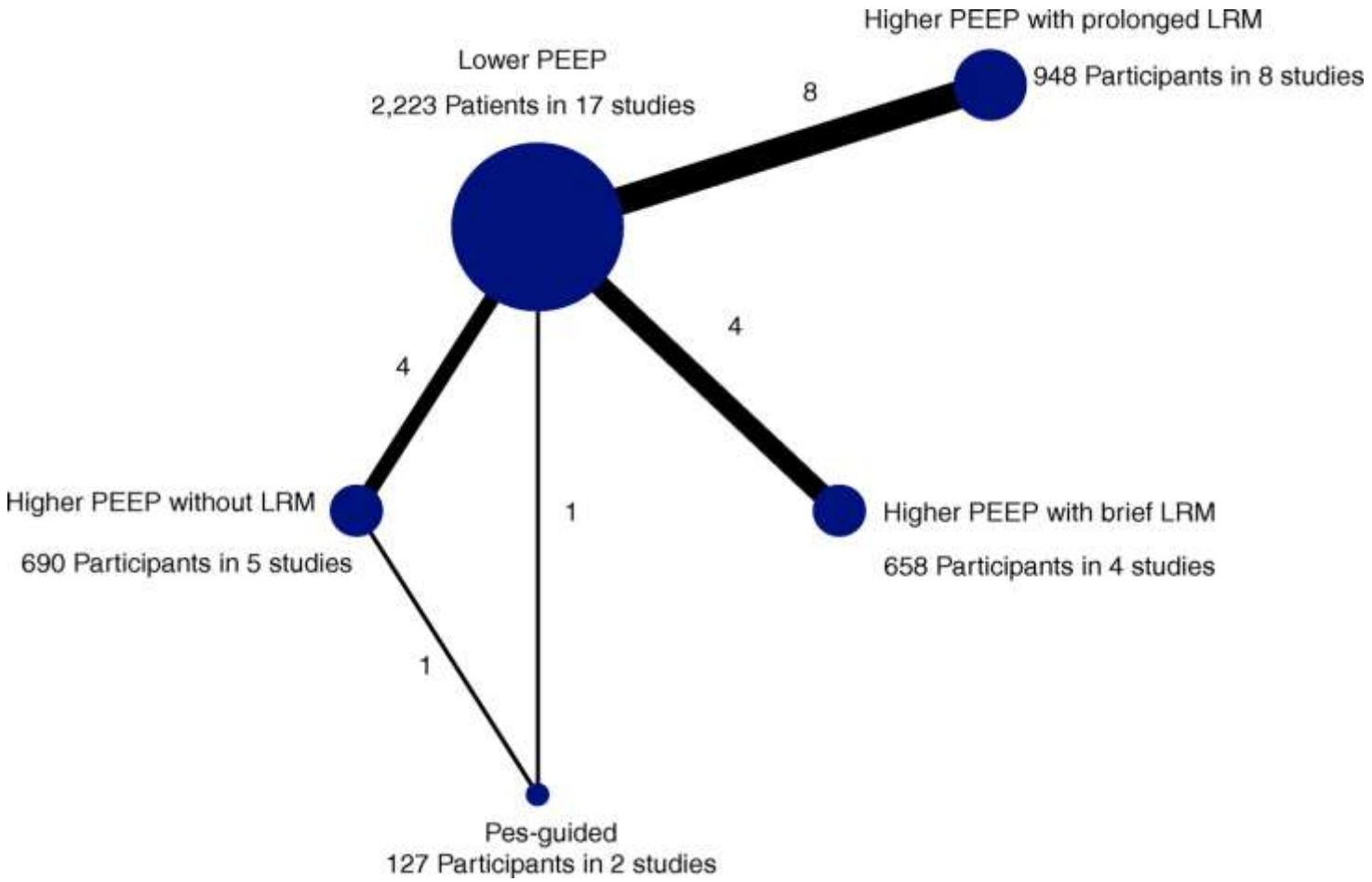
new ESICM guidelines on ARDS. ESICM 2023

Association of Positive End-Expiratory Pressure and Lung Recruitment Selection Strategies with Mortality in Acute Respiratory Distress Syndrome: A Systematic Review and Network Meta-analysis

Jose Dianti [1,2], Manuel Tisminetzky [1,2], Bruno L. Ferreyro [1,2,3], Marina Englesakis [4], Lorenzo Del Sorbo [1,2,5], Sachin Sud [6], Daniel Talmor [7], Lorenzo Ball [8], Maureen Meade [9,10], Carol Hodgson [11,12], Jeremy R. Beitler [13], Show All...

- **Objectives:** To compare the relative effects of different PEEP selection strategies on mortality in adults with moderate to severe ARDS
- 18 randomized trials (2004 -2020)
- 4,646 participants

Dianti, et al. (2022). Association of positive end-expiratory pressure and lung recruitment selection strategies with mortality in acute respiratory distress syndrome. AJRCCM, 205(11), 1300–1310.



Dianti, et al. (2022). Association of positive end-expiratory pressure and lung recruitment selection strategies with mortality in acute respiratory distress syndrome. AJRCCM, 205(11), 1300–1310.

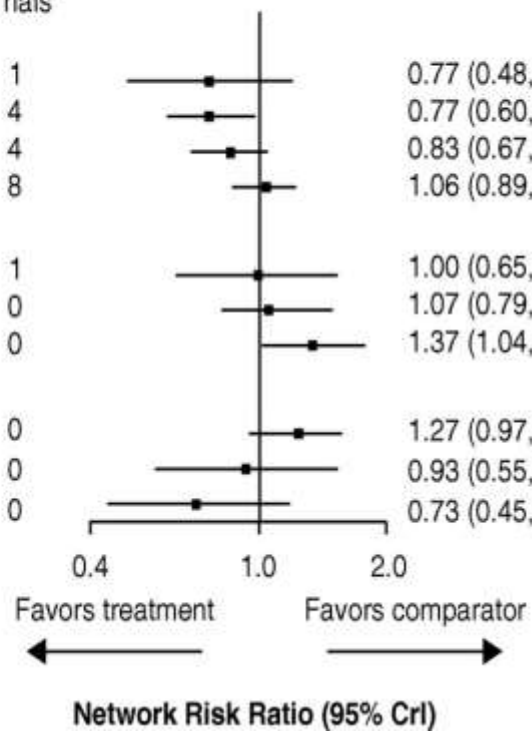
- Compared with a lower PEEP strategy, the posterior probability of mortality benefit from a higher PEEP without LRM strategy was 99% (risk ratio [RR], 0.77; 95% [CrI], 0.60–0.96
- The posterior probability of benefit of the esophageal pressure–guided strategy was 87% (RR, 0.77; 95% CrI, 0.48–1.22, moderate certainty)

Dianti, et al. (2022). Association of positive end-expiratory pressure and lung recruitment selection strategies with mortality in acute respiratory distress syndrome. AJRCCM, 205(11), 1300–1310.

- The posterior probability of increased mortality from a higher PEEP with prolonged LRM strategy was 77% (RR, 1.06; 95% CrI, 0.89–1.22, low certainty)
- Compared with a higher PEEP without LRM strategy, the posterior probability of increased mortality from a higher PEEP with prolonged LRM strategy was 99% (RR, 1.37; 95% CrI, 1.04–1.81, moderate certainty)
- In patients with moderate to severe ARDS, higher PEEP without LRM is associated with a lower risk of death than lower PEEP. A higher PEEP with prolonged LRM strategy is associated with increased risk of death when compared with higher PEEP without LRM

Dianti, et al. (2022). Association of positive end-expiratory pressure and lung recruitment selection strategies with mortality in acute respiratory distress syndrome. AJRCCM, 205(11), 1300–1310.

	Direct comparisons		Network Risk Ratio (95% CrI)	Absolute risk difference (95% CrI)	Posterior probabilities			Certainty
	Patients	Trials			RR < 1.0	RR > 1.0	ARR > 1%	
vs. Lower PEEP strategy								
Pes-guided	49	1	0.77 (0.48, 1.22)	–0.09 (–0.21, 0.09)	0.87	0.13	0.84	Moderate
Higher PEEP without LRM	1,162	4	0.77 (0.60, 0.96)	–0.09 (–0.16, –0.01)	0.99	0.01	0.98	High
Higher PEEP with brief LRM	1,335	4	0.83 (0.67, 1.02)	–0.07 (–0.13, 0.01)	0.96	0.04	0.94	Moderate
Higher PEEP with prolonged LRM	1,900	8	1.06 (0.89, 1.22)	0.02 (–0.04, 0.09)	0.23	0.77	0.15	Low
vs. Higher PEEP without LRM strategy								
Pes-guided	200	1	1.00 (0.65, 1.54)	0.00 (–0.11, 0.16)	0.50	0.50	0.44	Moderate
Higher PEEP with brief LRM	0	0	1.07 (0.79, 1.48)	0.02 (–0.08, 0.12)	0.32	0.68	0.25	Low
Higher PEEP with prolonged LRM	0	0	1.37 (1.04, 1.81)	0.11 (0.01, 0.21)	0.01	0.99	0.01	Moderate
Additional comparisons								
Higher PEEP with prolonged vs. brief LRM	0	0	1.27 (0.97, 1.64)	0.09 (–0.01, 0.18)	0.04	0.96	0.03	Low
Pes-guided vs. Higher PEEP with brief LRM	0	0	0.93 (0.55, 1.54)	–0.02 (–0.16, 0.17)	0.61	0.39	0.57	Low
Pes-guided vs. Higher PEEP with prolonged LRM	0	0	0.73 (0.45, 1.19)	–0.11 (–0.25, 0.08)	0.90	0.10	0.88	Low

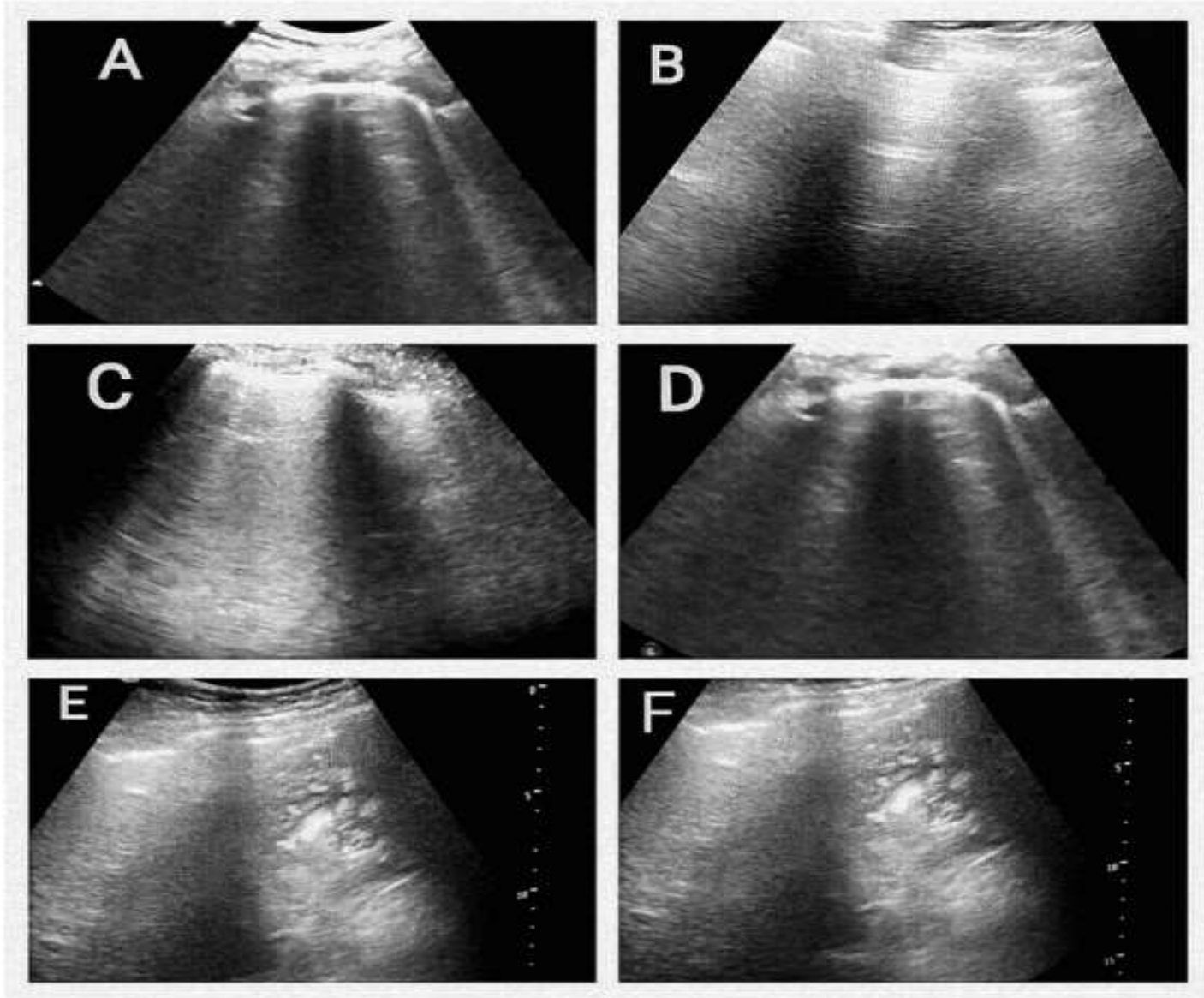


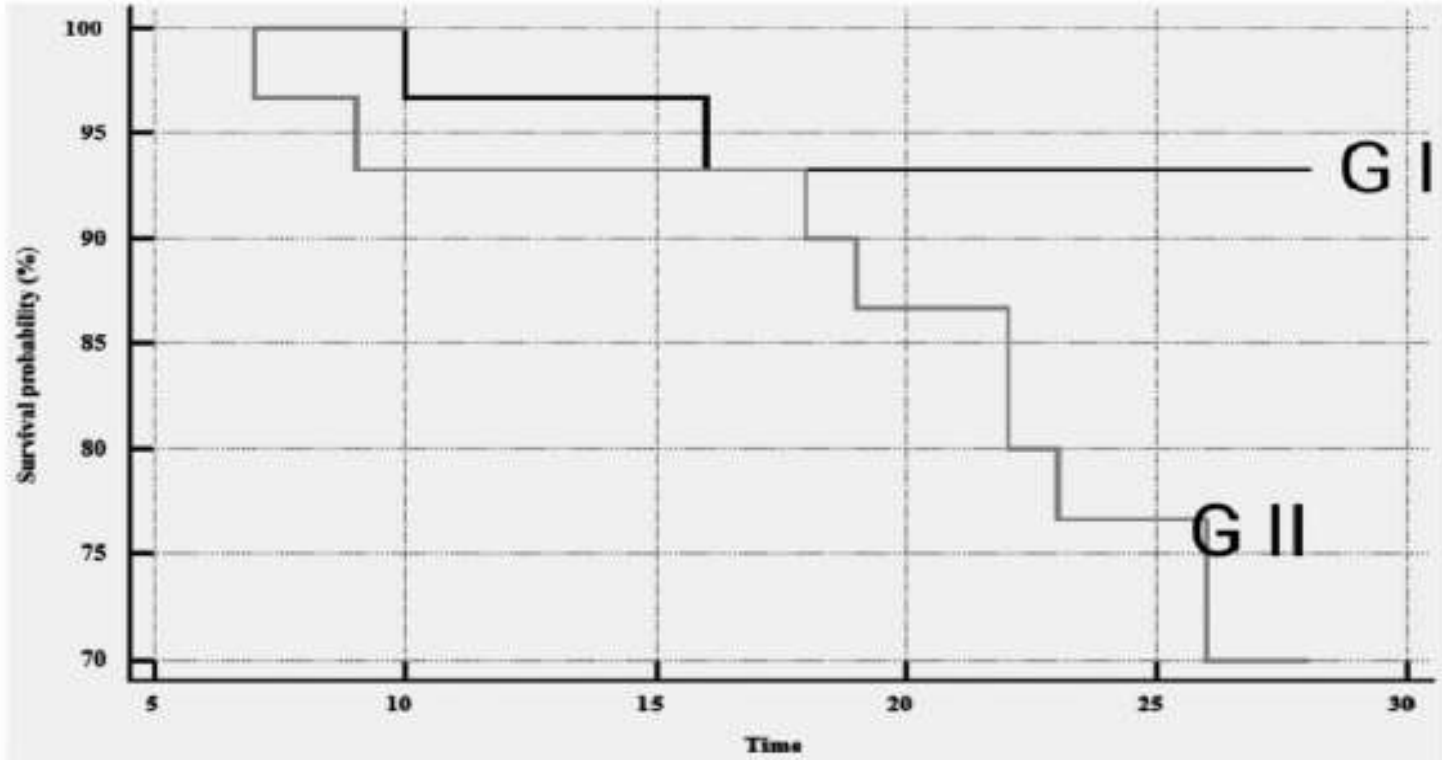
Lung ultrasound- versus FiO_2-guided PEEP in ARDS patients

Mai S. Salem, Hesham S. Eltatawy, Ahmed A. Abdelhafez and Salah El-din I. Alsherif

Department of Anesthesia, Surgical Intensive Care and Pain Medicine, Tanta University Hospitals, Tanta, Egypt

- RCT – 2020
- N = 60
- LUS-determined PEEP (group l) and FiO2-determined PEEP (group II)
- LUS-determined PEEP was based on the LUS aeration score
- Primary outcome was P/F ratio
- Secondary outcomes were; static compliance, 28-day mortality, duration of MV, and length of ICU stay


A
B
C
D
E
F


100
95
90
85
80
75
70
Survival probability (%)
5
10
15
20
25
30
Time
G I
G II

- P/F ratio was 266 ± 44.5 in group I, 233 ± 53.9 in group II (P<0.001)
- Static compliance was 54.8 ± 6.6 in group I, 45.9 ± 3.8 in group II(P<0.001)
- IQR of duration of MV was 4–6 with a median value of 5 in group l, 6–11.7 with a median value of 7.5 in group l
- 28-day mortality was 6.7% in group l, 30% in group ll

SOFA score			
Median	1.5	3	<0.001*
IQR	1–2	2–4	
Duration of MV(days)			
Median	8	12	<0.001*
IQR	4–6	6–11.7	
Length of ICU(days)			
Median	8	10	<0.001*
IQR	6–16	0–12	
Organ dysfunction Free days			
Median	18	10	<0.001*
IQR	16–19	0–12	
Ventilator free days			
Median	23	20	<0.001*
IQR	22–24	0–22	

Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome

Systematic Review and Meta-analysis

- To evaluate role of higher vs lower PEEP in adults with acute lung injury or ARDS who are receiving low Vt ventilation
- Randomized trials eligible for this review compared higher with lower levels of PEEP (min difference 3)
- Data from 2299 individual patients in 3 trials (LOVS, EXPRESS, ALVEOLI) were analyzed
- In ALVEOLI and LOVS trial PEEP levels were titrated to oxygenation using PEEP:FIO2 charts

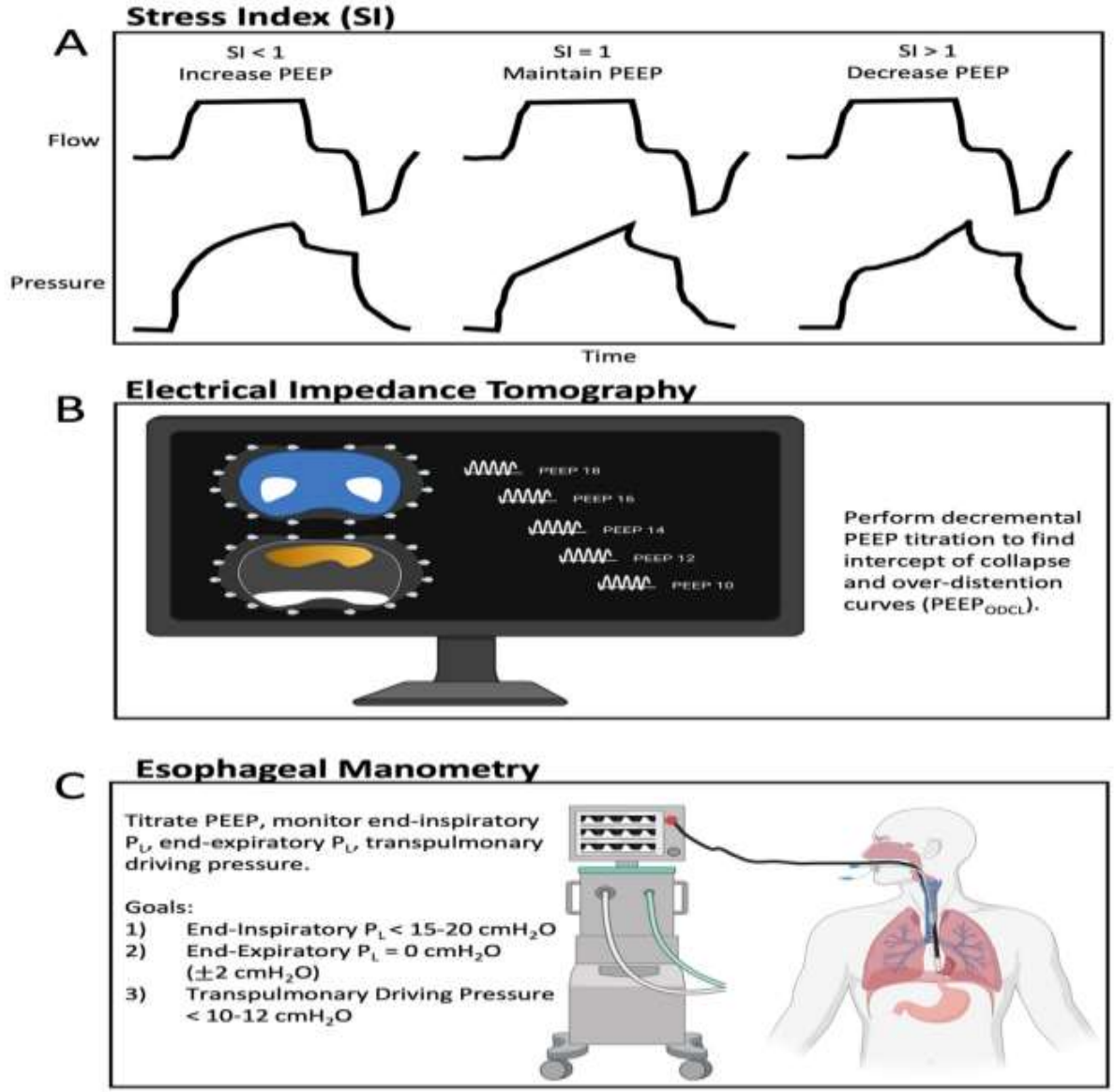
Briel, M., et al (2010a).. JAMA: 303(9), 865. https://doi.org/10.1001/jama.2010.218

Characteristic	Trial		
	ALVEOLI,[8] 2004	LOVS,[9] 2008	EXPRESS,[10] 2008
Inclusion criteria	Acute lung injury with PaO_2:FIO_2 ≤300[a]	Acute lung injury with PaO_2:FIO_2 ≤250[a]	Acute lung injury with PaO_2:FIO_2 ≤300[a]
Recruitment period	1999-2002	2000-2006	2002-2005
Recruiting hospitals (country)	23 (United States)	30 (Canada, Australia, Saudi Arabia)	37 (France)
Patients randomized to higher vs lower PEEP	276 vs 273	476 vs 509[b]	385 vs 383[c]
Validity			
Concealed allocation	Yes	Yes	Yes
Follow-up for primary outcome, %	100	100	100
Blinded data analysis	Yes	Yes	Yes
Stopped early	Stopped for perceived futility	No	Stopped for perceived futility
Experimental intervention	Higher PEEP according to FIO_2 chart, recruitment maneuvers for first 80 patients	Higher PEEP according to FIO_2 chart, required plateau pressures ≤40 cm H_2O, recruitment maneuvers	PEEP as high as possible without increasing the maximum inspiratory plateau pressure >28-30 cm H_2O
Control intervention	Conventional PEEP according to FIO_2 chart, required plateau pressures ≤30 cm H_2O, no recruitment maneuvers	Conventional PEEP according to FIO_2 chart, required plateau pressures ≤30 cm H_2O, no recruitment maneuvers	Conventional PEEP (5-9 cm H_2O) to meet oxygenation goals
Ventilator procedures	Target tidal volumes of 6 mL/kg of predicted body weight; plateau pressures ≤30 cm H_2O (with exception as above); respiratory rate ≤35/ min, adjusted to achieve arterial pH 7.30-7.45; ventilator mode: volume-assist control (except higher PEEP group in LOVS required pressure control); oxygenation goals: PaO_2 55-80 mm Hg and SPO_2 88%-95%; standardized weaning)		

Table 4. Clinical Outcomes in All Patients and Stratified by Presence of ARDS at Baseline

Outcomes	All Patients				With ARDS				Without ARDS			
	No. (%)				No. (%)				No. (%)			
	Higher PEEP (n = 1136)	Lower PEEP (n = 1163)	Adjusted RR (95% CI)[a]	*P* Value	Higher PEEP (n = 951)	Lower PEEP (n = 941)	Adjusted RR (95% CI)[a]	*P* Value	Higher PEEP (n = 184)	Lower PEEP (n = 220)	Adjusted RR (95% CI)[a]	*P* Value
Death in hospital	374 (32.9)	409 (35.2)	0.94 (0.86 to 1.04)	.25	324 (34.1)	368 (39.1)	0.90 (0.81 to 1.00)	.049	50 (27.2)	44 (19.4)	1.37 (0.98 to 1.92)	.07
Death in ICU[b]	324 (28.5)	381 (32.8)	0.87 (0.78 to 0.97)	.01	288 (30.3)	344 (36.6)	0.85 (0.76 to 0.95)	.001	36 (19.6)	37 (16.8)	1.07 (0.74 to 1.55)	.71
Pneumothorax between day 1 and day 28[c]	87 (7.7)	75 (6.5)	1.19 (0.89 to 1.60)	.24	80 (8.4)	64 (6.8)	1.25 (0.94 to 1.68)	.13	7 (3.8)	11 (5.0)	0.72 (0.37 to 1.39)	.33
Death after pneumothorax[c]	43 (3.8)	40 (3.5)	1.11 (0.73 to 1.69)	.63	41 (4.3)	35 (3.7)	1.20 (0.79 to 1.81)	.39	2 (1.1)	5 (2.3)	0.44 (0.08 to 2.35)[g]	.34
Days with unassisted breathing between day 1 and day 28, median (IQR)[d]	13 (0 to 22)	11 (0 to 21)	0.64 (−0.12 to 1.39)[e]	.10	12 (0-21)	7 (0-20)	1.22 (0.39 to 2.05)[e]	.004	17 (0-23)	19 (5.5-24)	−1.74 (−3.60 to 0.11)[e]	.07
Total use of rescue therapies[f]	138 (12.2)	216 (18.6)	0.64 (0.54 to 0.75)	<.001	130 (13.7)	200 (21.3)	0.63 (0.53 to 0.75)	<.001	8 (4.4)	16 (7.3)	0.60 (0.25 to 1.43)[g]	.25
Death after rescue therapy[f]	85 (7.5)	132 (11.3)	0.65 (0.52 to 0.80)	<.001	82 (8.6)	124 (13.2)	0.66 (0.52 to 0.82)	<.001	3 (1.6)	8 (3.6)	0.37 (0.10 to 1.46)[g]	.15
Use of vasopressors	722 (63.6)	759 (65.3)	0.93 (0.75 to 1.14)[g]	.49	627 (65.9)	647 (68.8)	0.90 (0.72 to 1.13)[g]	.37	95 (51.6)	111 (50.5)	0.92 (0.56 to 1.50)[g]	.72

Advanced Methods for Individualized PEEP Titration



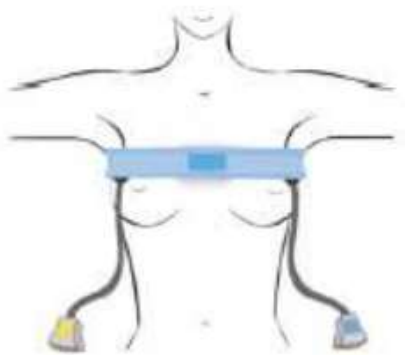
John Groteberg et al critical care

Electrical Impedance Tomography(EIT) in ARDS

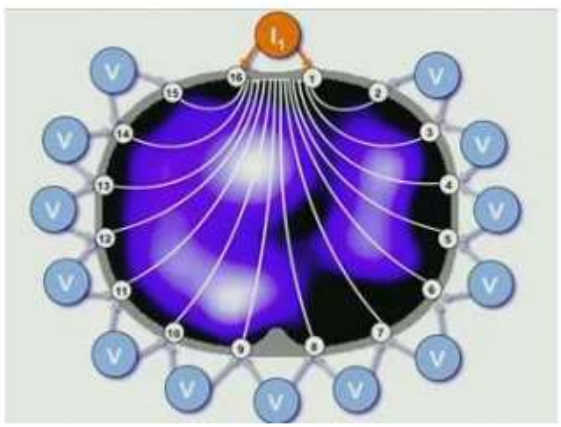
- EIT is a non invasive bedside radiation free imaging tool

- Images generated by EIT can help in real time monitoring of pulmonary ventilation

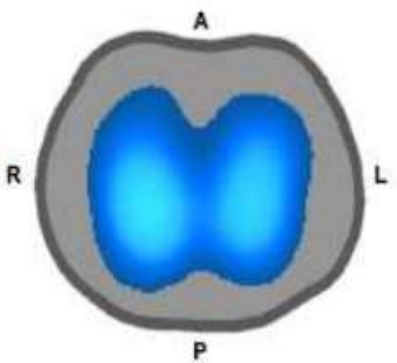
Brief small alternating currents Delivered via electrodes attached to band applied to chest



Voltages read by electrodes depends upon resistivity/impedance of lung tissue



At end of one breathing cycle Voltages recorded are used to generate a pixel image based on prespecified reconstruction algorithm



Bachmann et al. Critical Care (2018)

Role Of EIT In ARDS

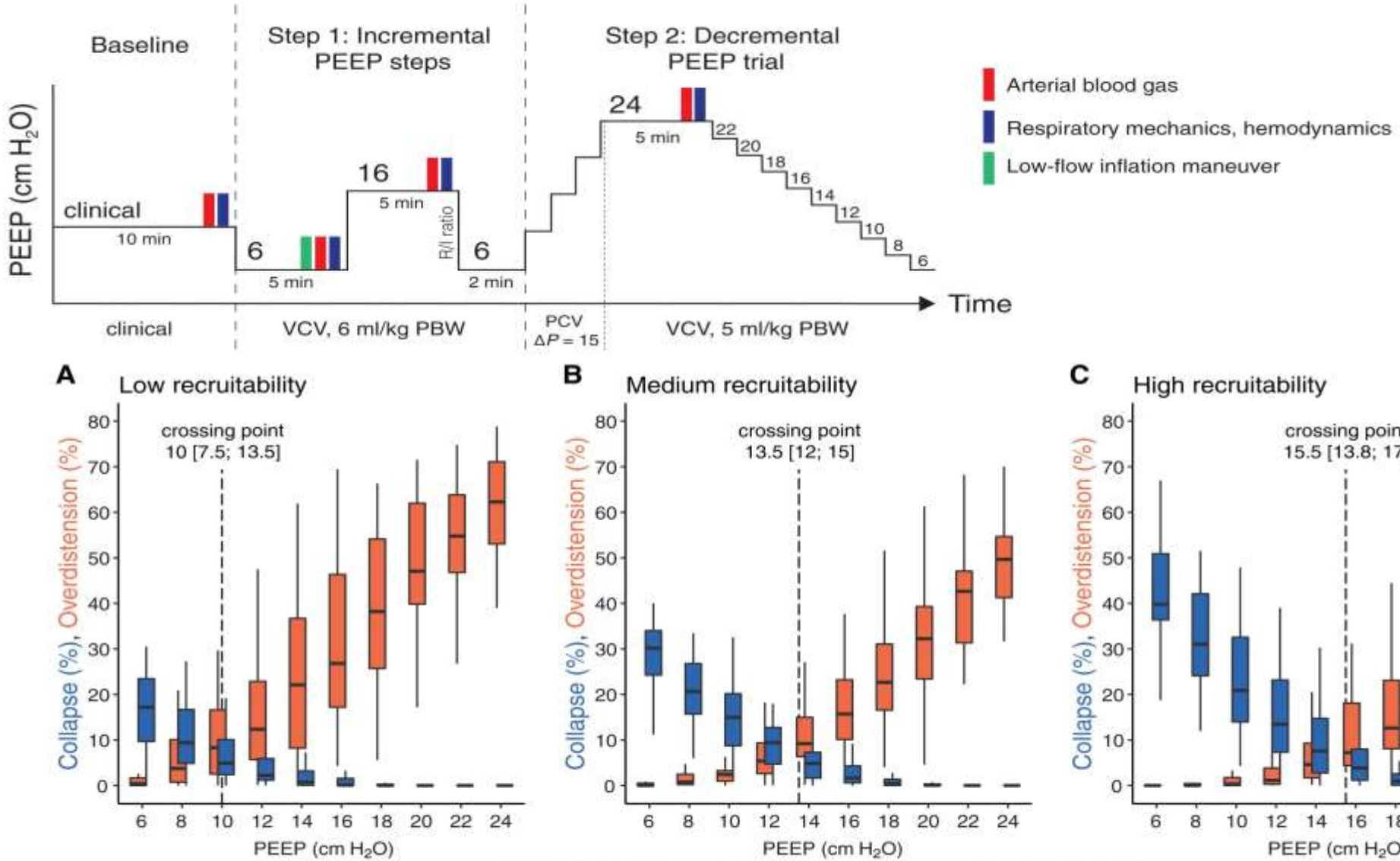
- ARDS is a heterogenous condition with regional difference in ventilation
- Ventilation map can help detect these regional difference
- EIT plethysmography can help assess changes in these areas during recruitment manoeuvre and aid in PEEP titration
- EIT derived changes in lung volume and images have been found to correlate with lung mechanic indices and CT images

Lowhagen K, et al. Acta Anaesthesiol Scand. 2011;55:165–74.

🔓 Lung Recruitment Assessed by Electrical Impedance Tomography (RECRUIT): A Multicenter Study of COVID-19 Acute Respiratory Distress Syndrome

- **Rationale:** Defining lung recruitability is needed for safe PEEP selection in mechanically ventilated patients
- **Objectives:** To describe the range of recruitability using EIT, effects of PEEP on recruitability, respiratory mechanics and gas exchange, and a method to select optimal EIT-based PEEP
- Included 108 patients of COVID 19 with mod to severe ards
- EIT-based optimal PEEP was defined as the crossing point of the overdistension and collapse curves during a decremental PEEP trial

Annemijn H. Jonkman et al ATS Journal 2023



Annemijn H. Jonkman et al ATS Journal 2023

- Patients were classified as low, medium, or high recruiters Recruitability varied from 0.3% to 66.9% and was unrelated to ards severity
- Median EIT-based PEEP differed between groups: 10 versus 13.5 versus 15.5 cm H_2O for low versus medium versus high recruitability ($P < 0.05$)

Annemijn H. Jonkman et al ATS Journal 2023

EP VENT 1 & 2

STUDY	EP VENT 1	EP VENT 2
Type	Single centre Pilot study	Multicentre phase 2 RCT
Population	ALI/ARDS(AECC) N=61	Mod.- Sev ARDS (P/F<200 Berlin definition) N=202
Intervention	PEEP guided by Pes vs Empirical PEEP FiO2 table PTPinsp <25	PEEP guided by Pes vs High PEEP FiO2 table PTPinsp <20 PTPexp >0
Outcome	Primary : Improvement in P/F Secondary : Days free from MV Deaths at day 28 LOS in ICU	Primary : No. of Deaths at day 28 Days free from MV at day 28 Secondary : 60 d mortality 180 d mortality LOS in hospital and ICU

Results	EP VENT 1	EP VENT 2
28 d Mortality	17% v/s 39% p=0.055	32.4% vs 30.6% p=0.88
Ventilator Free days to day 28	11.5d vs 7d p=0.5	15.5d vs 17.5d p=0.93
Hospital LOS to day 28	-	16d vs 15d p=0.58
ICU LOS to day 28	15.5d vs 13d p=0.16	10d vs 9.5d p=0.25
Improvement in P/F	88mmHg in Intervention arm	N/A

Routine use of Pes guided PEEP titration offered no benefit compared to conventional PEEP FiO_2 titration

Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial

- Randomized patients (n=400)to either standard LTV or a personalized treatment strategy - Based on radiological sub-phenotype (focal or diffuse pathology on cxr)
- Patients with focal ARDS received a Vt of 8 mL/kg, low PEEP, and early prone position if needed

Constantin et al., 2019 *The Lancet. Respiratory medicine*, 7(10), pp. 870–880

- Patients with non-focal ARDS received a tidal volume of 6 mL/kg, along with recruitment maneuvers and high PEEP
- No difference in 90-day mortality - (hazard ratio [HR] 1·01; 95% CI 0·61–1·66; p=0·98)
- Misclassification of patients as having focal or non-focal ARDS by the investigators was observed in 85 (21%) of 400 patients
- Results were “positive” when misclassified patients were excluded(p0.0012)

Constantin et al., 2019 *The Lancet. Respiratory medicine*, 7(10), pp. 870–880

APRV(Airway Pressure Release Ventilation)

- Delivery of continuous positive airway pressure with a brief release phase

- Hypothesized to improve gas exchange by alveolar recruitment

Study	Population	Intervention	Outcome
Putensen et al. 2001	N=30 Trauma rel. ARDS	APRV PCV	No. of ventilator days 15d vs 21d ICU stay 23d vs 30d
Maxwell et al. 2016	N= 63 Trauma rel. ARDS	APRV LTV	No. of ventilator days 15d vs 21d Mortality 6.45% vs 6.25%
Zhou et al.2017	Single centre N=138 (~70% Extrapulmonary cause)	APRV LTV	Ventilator free days 19d vs 2d Length of ICU stay 15d vs 20d Mortality 23.9% vs 37.3%

- High PEEP without LRM to be used
- High PEEP with prolonged LRM – To be avoided
- High PEEP with brief LRM - ?insuff data ?mortality benefit
- Personalized PEEP strategy – Pes, EIT, LUS etc

ATS guidelines on ARDS 2024

- We suggest using higher PEEP without lung recruitment maneuvers (LRMs) as opposed to lower PEEP in patients with moderate to severe ARDS (conditional recommendation, low to moderate certainty)
- We recommend against using prolonged LRMs in patients with moderate to severe ARDS (strong recommendation, moderate certainty)

(Qadir *et al.*, 2024) “An update on the management of adult patients with ards:, 209(1), pp. 24–36. doi: 10.1164/rccm.202311-2011st.

7. Prone positioning

PROSEVA Trial

Study	Population	Intervention	Outcome
Multicentre RCT	N = 466 P:F <150, Fio2 >60%, PEEP≥ , MV <36 hrs	PPV (Atleast 16 hrs) Vs Supine LTV	-28-day mortality 16% vs 32 % -HR for death in prone grp – 0.39 -Unadjusted 90 day mortality – 23.6 % vs 41%(HR – 0.44)

Claude Guérin et al NEJM 2013

- The criteria for stopping prone treatment - any of the following:

  Improvement in oxygenation (defined as a PaO_2:FiO_2 ratio of ≥150 mm Hg, with a PEEP of ≤10 cm of water and an FiO_2 of ≤0.6; in the prone group

- had to be met in the supine position at least 4 hours after the end of the last prone session
- Patients in the supine group could not be crossed over to the prone group except as a rescue measure in case of life-threatening hypoxemia

Claude Guérin et al NEJM 2013

Table 3. Primary and Secondary Outcomes According to Study Group.*

Outcome	Supine Group (N=229)	Prone Group (N=237)	Hazard Ratio or Odds Ratio with the Prone Position (95% CI)	P Value
Mortality — no. (% [95% CI])				
At day 28				
Not adjusted	75 (32.8 [26.4–38.6])	38 (16.0 [11.3–20.7])	0.39 (0.25–0.63)	<0.001
Adjusted for SOFA score†			0.42 (0.26–0.66)	<0.001
At day 90				
Not adjusted	94 (41.0 [34.6–47.4])	56 (23.6 [18.2–29.0])	0.44 (0.29–0.67)	<0.001
Adjusted for SOFA score†			0.48 (0.32–0.72)	<0.001
Successful extubation at day 90 — no./total no. (% [95% CI])	145/223 (65.0 [58.7–71.3])	186/231 (80.5 [75.4–85.6])	0.45 (0.29–0.70)	<0.001
Time to successful extubation, assessed at day 90 — days				
Survivors	19±21	17±16		0.87
Nonsurvivors	16±11	18±14		
Length of ICU stay, assessed at day 90 — days				
Survivors	26±27	24±22		0.05
Nonsurvivors	18±15	21±20		
Ventilation-free days				
At day 28	10±10	14±9		<0.001
At day 90	43±38	57±34		<0.001
Pneumothorax — no. (% [95% CI])	13 (5.7 [3.9–7.5])	15 (6.3 [4.9–7.7])	0.89 (0.39–2.02)	0.85
Noninvasive ventilation — no./total no. (% [95% CI])				
At day 28	10/212 (4.7 [1.9–7.5])	4/228 (1.8 [0.1–3.5])	0.36 (0.07–3.50)	0.11
At day 90	3/206 (1.5 [0.2–3.2])	4/225 (1.8 [0.1–3.5])	1.22 (0.23–6.97)	1.00
Tracheotomy — no./total no. (% [95% CI])				
At day 28	12/229 (5.2 [2.3–8.1])	9/237 (3.8 [1.4–6.0])	0.71 (0.27–1.86)	0.37
At day 90	18/223 (8.1 [4.5–11.7])	15/235 (6.4 [3.3–9.5])	0.78 (0.36–1.67)	0.59

Claude Guérin et al NEJM 2013

- Guidelines recommend using prone position as compared to supine position for patients with moderate-severe ARDS (defined as PaO2/FiO2 <150 and PEEP > 5 despite optimization of ventilatory setting) to reduce mortality***
- This recommendation applies also to ARDS from COVID-19** - suggest awake prone positioning for non-intubated patients to reduce intubation

new ESICM guidelines on ARDS. ESICM 2023

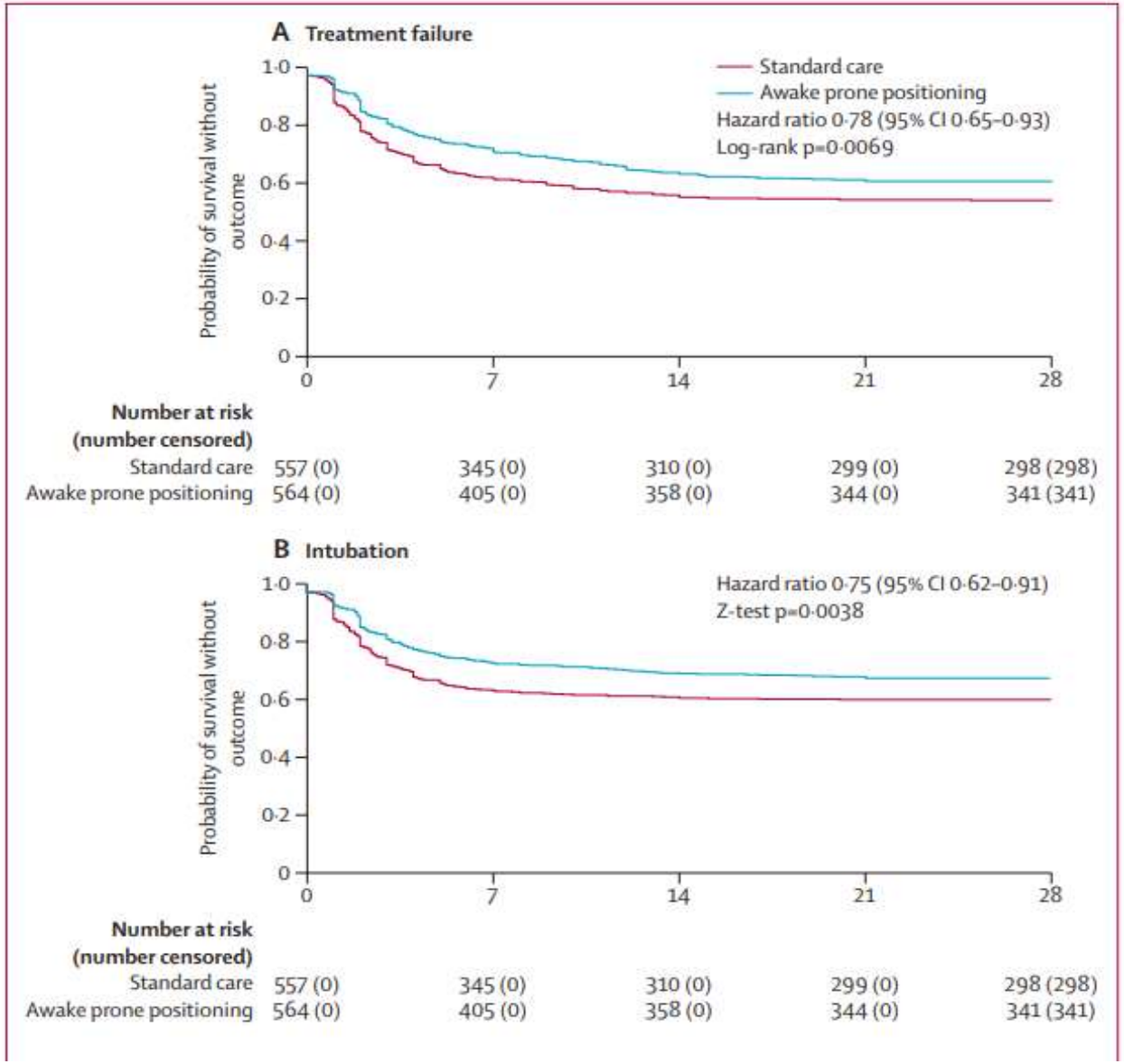
Awake prone positioning for COVID-19 acute hypoxemic respiratory failure: a randomized, controlled, multinational, open-label meta-trial

- Collaborative meta-trial of six randomized controlled open-label superiority trials
- Adults who required respiratory support with a HFNC for AHRF due to COVID-19 were randomly assigned to awake prone positioning or standard care
- The primary composite outcome was treatment failure, defined as the proportion of patients intubated or dying within 28 days of enrolment
- 1126 patients were enrolled and randomly assigned to awake prone positioning (n=567) or standard care (n=559)

Ehrmann, S. et al. (2021) “Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial,” The Lancet. Respiratory medicine, 9(12), pp. 1387–1395

- Treatment failure occurred in 223 (40%) of 564 patients assigned to awake prone positioning and in 257 (46%) of 557 patients assigned to standard care (relative risk 0·86 [95% CI 0·75–0·98])
- The hazard ratio (HR) for intubation was 0·75 (0·62–0·91), and the HR for mortality was 0·87 (0·68–1·11) with awake prone positioning compared with standard care within 28 days of enrolment

Ehrmann, S. et al. (2021) “Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial,” The Lancet. Respiratory medicine, 9(12), pp. 1387–1395



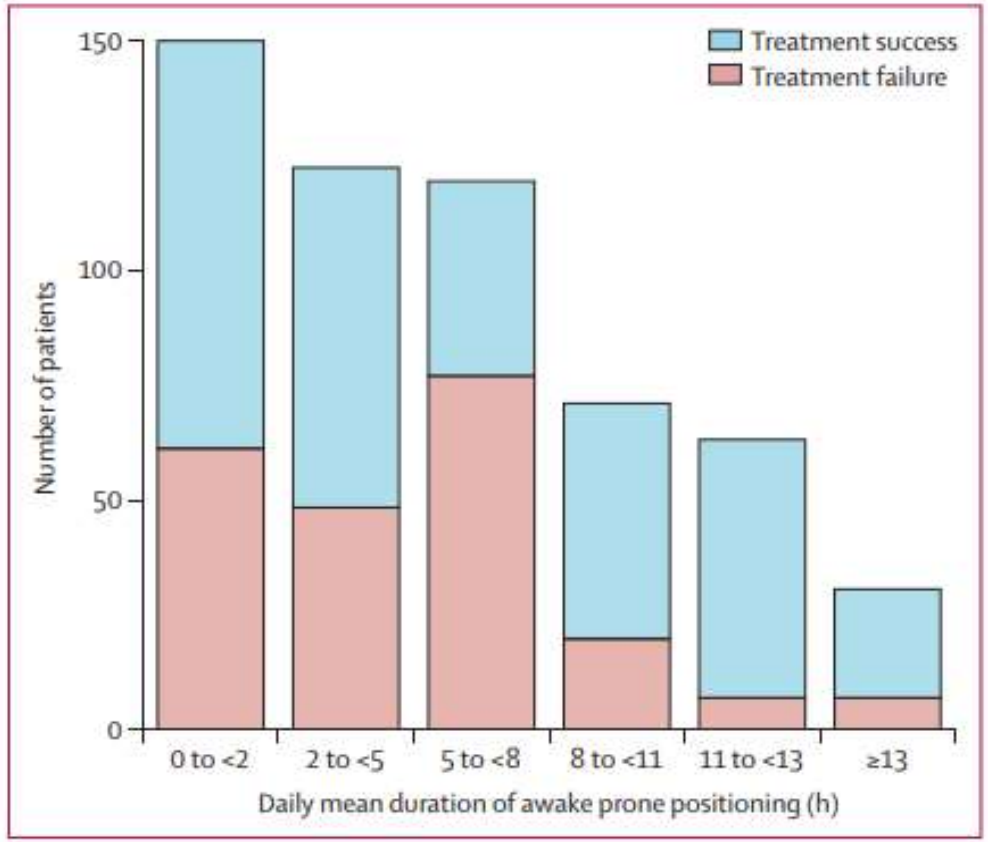


***Figure 4*: Daily mean duration of prone positioning and outcomes in patients allocated to awake prone positioning**

8. NMBA

Study/Characteristics	ACURASYS(2010)	ROSE(2019)
Type	Multicentre RCT **Double Blind** N=340 P/F<150; PEEP>5 (AECC) **Mean PEEP – 9.2 cm H2o**	Multicentre RCT **Open label** N=1006 Mod-sev ARDS(Berlin) P/F or S/F <150; PEEP >8 **Mean PEEP 12.6 cm H2o**
Intervention	**Deep sedation** + early NMB (178) vs **Deep sedation**	**Deep sedation** + early NMB(501) vs **Light sedation** alone(505)
	ARMA PEEP FIO2 table Proning in – 30%	HIGH PEEP FIO2 table Proning in – 16%
28 day mortality	23.7% vs 33.3%	36.7% vs 37%
90 day mortality	31.6% vs 40.7%(p=0.04)	41.5% vs 42.8% (p=0.93)

Neuromuscular blockade in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials

- Studied RCTs evaluating 28-day mortality in ARDS patients treated with NMBA within 48 h
- From 2675 studies, five RCTs were included in the analysis, for a total of 1461 patients
- Mean PaO2/ FIO2 of 104 ± 35 mmHg

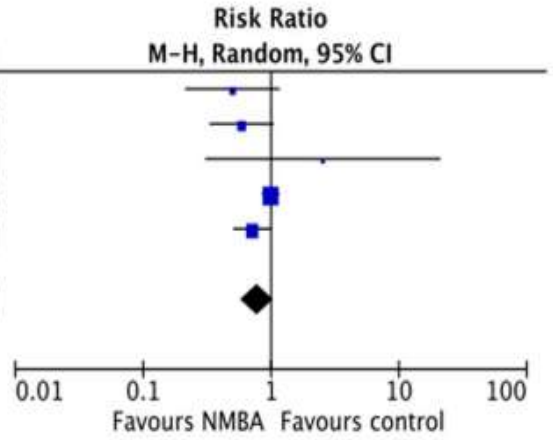
Ho et al. Journal of Intensive Care (2020)

28-day mortality

Study or Subgroup	NBMA Events	NBMA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Forel 2006	5	18	10	18	9.8%	0.50 [0.21, 1.17]
Gainnier 2004	10	28	17	28	17.1%	0.59 [0.33, 1.05]
Guervilly 2017	3	13	1	11	1.9%	2.54 [0.31, 21.06]
Moss 2019	184	501	187	505	41.8%	0.99 [0.84, 1.17]
Papazian 2010	42	177	54	162	29.4%	0.71 [0.51, 1.00]
Total (95% CI)		**737**		**724**	**100.0%**	**0.78 [0.58, 1.06]**
Total events	244		269			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.01$, df = 4 (P = 0.09); $I^2 = 50\%$

Test for overall effect: Z = 1.60 (P = 0.11)

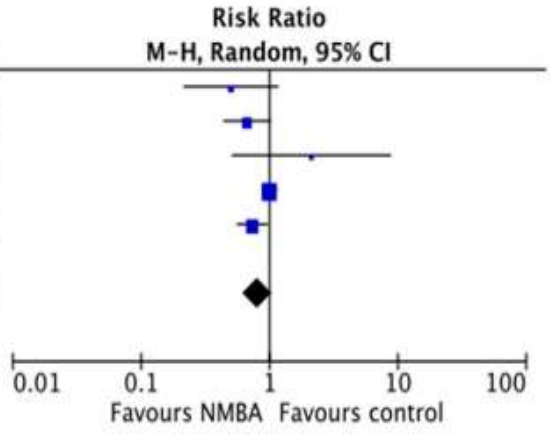


90-day mortality

Study or Subgroup	NBMA Events	NBMA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Forel 2006	5	18	10	18	7.9%	0.50 [0.21, 1.17]
Gainnier 2004	14	28	21	28	20.5%	0.67 [0.43, 1.02]
Guervilly 2017	5	13	2	11	3.2%	2.12 [0.51, 8.84]
Moss 2019	213	501	216	505	38.9%	0.99 [0.86, 1.15]
Papazian 2010	56	177	70	162	29.5%	0.73 [0.55, 0.97]
Total (95% CI)		**737**		**724**	**100.0%**	**0.81 [0.62, 1.06]**
Total events	293		319			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 9.03$, df = 4 (P = 0.06); $I^2 = 56\%$

Test for overall effect: Z = 1.54 (P = 0.12)



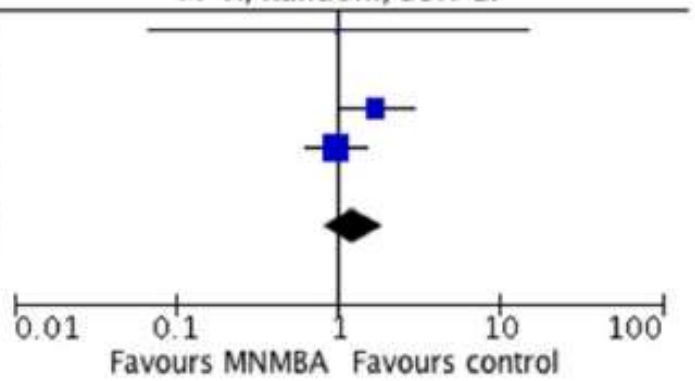
Ho et al. Journal of Intensive Care (2020)

ICU weakness day 28

Study or Subgroup	NMBA Events	NMBA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Forel 2006	1	18	1	18	2.4%	1.00 [0.07, 14.79]
Gainnier 2004	0	28	0	28		Not estimable
Moss 2019	22	47	14	51	42.6%	1.71 [0.99, 2.93]
Papazian 2010	28	89	25	77	55.1%	0.97 [0.62, 1.51]
Total (95% CI)		**182**		**174**	**100.0%**	**1.23 [0.81, 1.88]**
Total events	51		40			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.53$, df = 2 (P = 0.28); $I^2 = 21\%$

Test for overall effect: Z = 0.98 (P = 0.33)

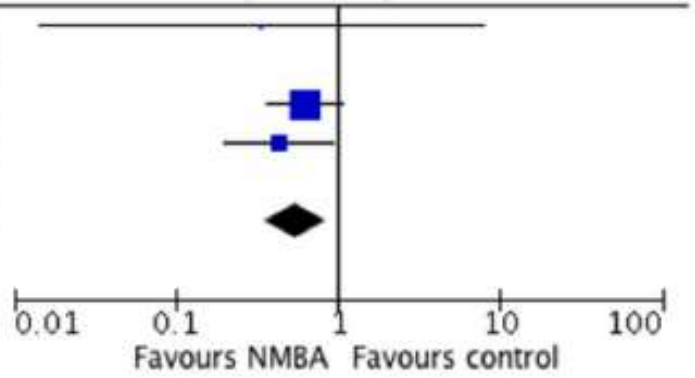


Barotrauma

Study or Subgroup	NMBA Events	NMBA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gainnier 2004	0	28	1	28	1.9%	0.33 [0.01, 7.85]
Guervilly 2017	0	13	0	11		Not estimable
Moss 2019	20	501	32	505	65.0%	0.63 [0.37, 1.09]
Papazian 2010	9	178	19	162	33.1%	0.43 [0.20, 0.93]
Total (95% CI)		**720**		**706**	**100.0%**	**0.55 [0.35, 0.85]**
Total events	29		52			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.73$, df = 2 (P = 0.70); $I^2 = 0\%$

Test for overall effect: Z = 2.68 (P = 0.007)



Ho et al. Journal of Intensive Care (2020)

ATS guidelines on ARDS 2024

- We suggest using neuromuscular blockers in patients with early severe ARDS (conditional recommendation, low certainty of evidence)

- ESICM guidelines – 2023
- We recommend against the routine use of continuous infusions of NMBA to reduce mortality in patients with moderate-to-severe ARDS not due to COVID-19

Role of NMB

- NMB is not routinely recommended but can be used to tackle asynchrony – not controlled by sedation

9. ECMO

	CESAR Trial (2009)	EOLIA Trial (2018)
Study	Multicentre RCT	Multicentre RCT
Population	N = 180	N = 249
Intervention	ECMO **(24% Did not receive ECMO)** Vs CMV**(LTV not used in all patients)**	ECMO vs CMV(adhere to LTV) **Crossover (Rescue ECMO allowed – 28%)**
Inclusion Criteria	**MV<7d** **Murray score >3; pH<7.2**	**MV<7d** **P/F <50 (3hrs), P/F <80 (6hrs), pH<7.25 (6hrs)**
Primary outcome	6 month mortality 47% vs 63%, RR-0.69 (P=0.03)	60 d mortality 35% vs 46%, RR-0.76 (p=0.09) **44% of patients who received Rescue ECMO survived**
Cointerventions	PPV(4 vs 42%)	PPV -90%, NMB – 100% used

Meta Analysis ECMO In ARDS – Effect On 30d Mortality

	ECMO		CMV		Weight (%)	Risk ratio (95% CI)
	Events	Total	Events	Total		
Peek et al (2009)[3]	29	90	44	90	21·8%	0·66 (0·46–0·95)
Noah et al (2011)[5]	11	75	31	75	14·4%	0·35 (0·19–0·65)
Pham et al (2013)[6]	26	52	21	52	19·7%	1·24 (0·81–1·90)
Tsai et al (2015)[18]	22	45	34	45	22·7%	0·65 (0·46–0·91)
Combes et al (2018)[22]	32	124	46	125	21·4%	0·70 (0·48–1·02)
Combined	**120**	**386**	**176**	**387**	**100·0%**	**0·69 (0·50–0·95)**

Heterogeneity: τ^2=0·08; χ^2=11·92, df=4, (p=0·02); I^2=66%
Test for overall effect: Z=2·31 (p=0·02)

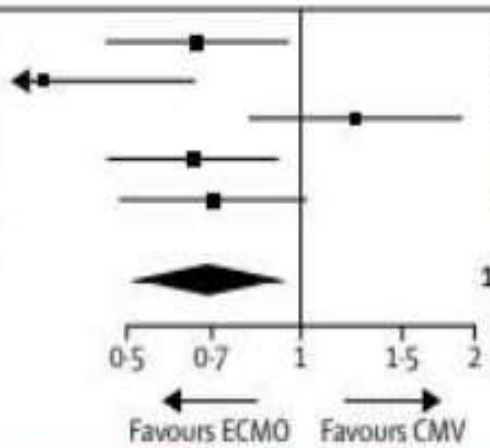


Figure 5: **Forest plot of 30-day mortality across all studies of ECMO vs CMV in adults with severe acute respiratory distress syndrome**

Munshi et al Lancet 2019

Role of ECMO

- ECMO can be considered an effective rescue strategy in patients with severe ARDS in ECMO-equipped centres

ESICM Guidelines on ARDS 2023

- Recommend that patients with severe ARDS as defined by the EOLIA trial eligibility criteria, should be treated with ECMO in an ECMO center***

new ESICM guidelines on ARDS, ESICM.2023

10. Corticosteroids

Dexamethasone in Hospitalized Patients with Covid-19

Author: The RECOVERY Collaborative Group* Author Info & Affiliations

Published July 17, 2020 | N Engl J Med 2021;384:693-704 | DOI: 10.1056/NEJMoa2021436

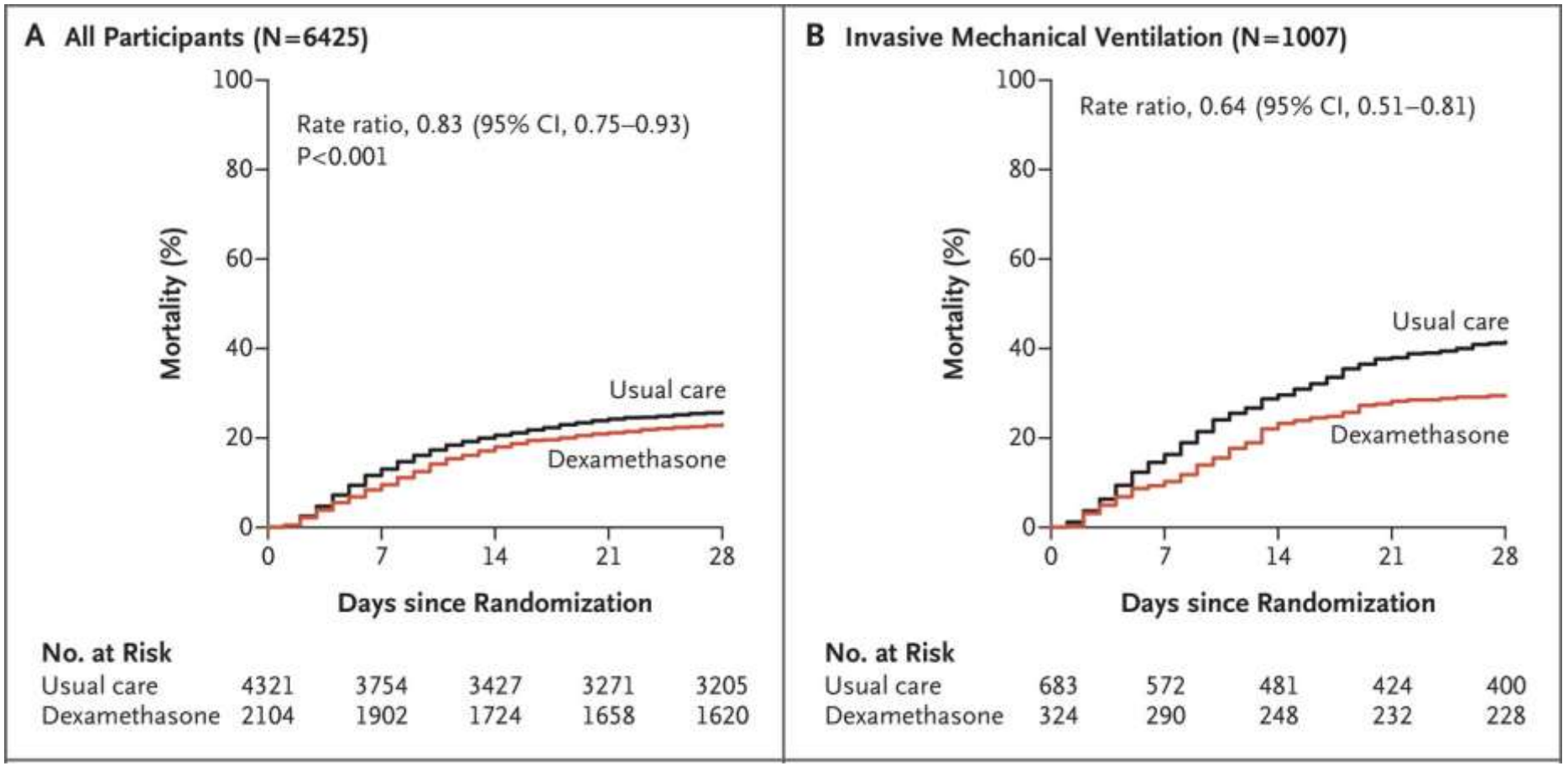
VOL. 384 NO. 8

- Patients was randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone
- The primary outcome was 28-day mortality
- 2104 patients were assigned to receive dexamethasone and 4321 were assigned to receive usual care

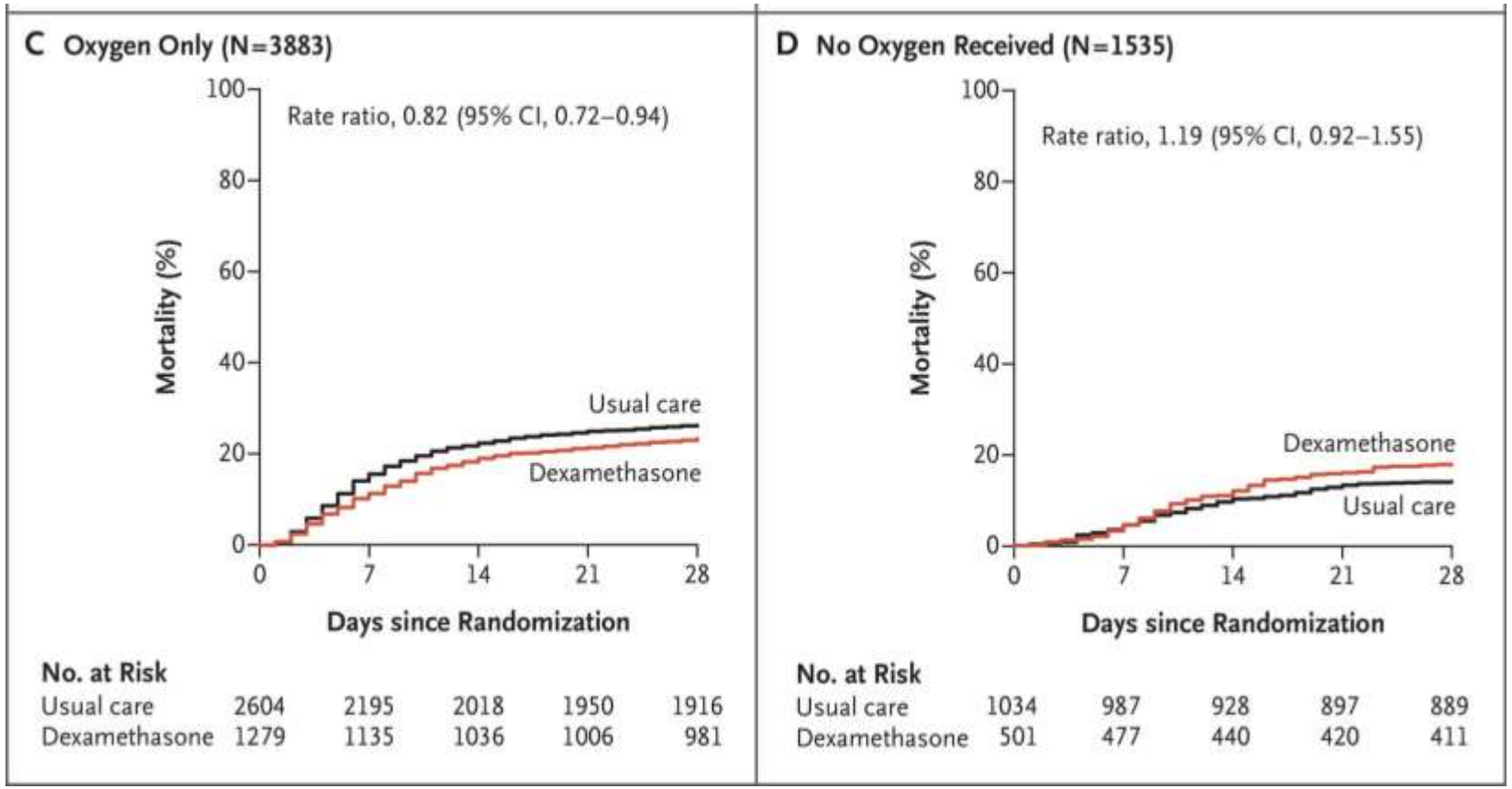
The RECOVERY Collaborative Group (2021) “Dexamethasone in hospitalized patients with covid-19,” NEJM, 384(8), pp. 693–704. doi: 10.1056/nejmoa2021436.

- Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% [CI], 0.75 to 0.93; P<0.001)
- The greatest absolute and proportional benefit among patients who were receiving invasive mechanical ventilation
- In the dexamethasone group, the incidence of death was lower among patients receiving invasive MV (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81)
- and in those receiving oxygen without invasive MV (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94

The RECOVERY Collaborative Group (2021) “Dexamethasone in hospitalized patients with covid-19,” NEJM, 384(8), pp. 693–704. doi: 10.1056/nejmoa2021436.



The RECOVERY Collaborative Group (2021) “Dexamethasone in hospitalized patients with covid-19,” NEJM, 384(8), pp. 693–704. doi: 10.1056/nejmoa2021436.



The RECOVERY Collaborative Group (2021) “Dexamethasone in hospitalized patients with covid-19,” NEJM, 384(8), pp. 693–704. doi: 10.1056/nejmoa2021436.

Table 2. Primary and Secondary Outcomes and Prespecified Subsidiary Clinical Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
		no./total no. of patients (%)	
Primary outcome			
Death at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1416/2104 (67.3)	2748/4321 (63.6)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	462/1780 (26.0)	1003/3638 (27.6)	0.93 (0.85–1.01)
Invasive mechanical ventilation	110/1780 (6.2)	298/3638 (8.2)	0.79 (0.64–0.97)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)
Subsidiary clinical outcomes			
Use of ventilation‡	25/501 (5.0)	65/1034 (6.3)	0.84 (0.54–1.32)
Noninvasive ventilation	20/501 (4.0)	57/1034 (5.5)	0.77 (0.47–1.26)
Invasive mechanical ventilation	9/501 (1.8)	19/1034 (1.8)	1.07 (0.49–2.34)
Successful cessation of invasive mechanical ventilation§	160/324 (49.4)	268/683 (39.2)	1.47 (1.20–1.78)
Renal-replacement therapy¶	89/2034 (4.4)	314/4194 (7.5)	0.61 (0.48–0.76)

The RECOVERY Collaborative Group (2021) “Dexamethasone in hospitalized patients with covid-19,” NEJM, 384(8), pp. 693–704. doi: 10.1056/nejmoa2021436.

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

*Jesús Villar, Carlos Ferrando, Domingo Martínez, Alfonso Ambrós, Tomás Muñoz, Juan A Soler, Gerardo Aguilar, Francisco Alba, Elena González-Higueras, Luís A Conesa, Carmen Martín-Rodríguez, Francisco J Díaz-Domínguez, Pablo Serna-Grande, Rosana Rivas, José Ferreres, Javier Belda, Lucía Capilla, Alec Tallet, José M Añón, Rosa L Fernández, Jesús M González-Martín for the dexamethasone in ARDS network**

- Multicenter, randomized controlled trial in a network of 17 intensive care units (ICUs)
- N = 277, 139 in dexa group, 138 in control group
- Moderate-to-severe ARDS (defined by P:F ratio of ≤ 200 assessed with a PEEP of ≥ 10 cm H2O and FiO2 of ≥ 0·5 at 24 h after ARDS onset)
- Patients in the dexamethasone group received an IV dose of 20 mg od from day 1 to 5, which was reduced to 10 mg od from day 6 to 10 (1st dose received immediately – not >30 hrs)
- Patients in both groups were ventilated with lung-protective mechanical ventilation
- Primary outcome was the number of ventilator-free days at 28 days
- Secondary outcome was all-cause mortality 60 days after randomization

Villar, J. et al. (2020) "Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial," The Lancet. Respiratory medicine, 8(3), pp. 267–276. doi: 10.1016/s2213-2600(19)30417-5.

	Dexamethasone group (n=139)	Control group (n=138)	Between-group difference (95% CI)	p value
Ventilator-free days at 28 days	12·3 (9·9)	7·5 (9·0)	4·8 (2·57 to 7·03)	<0·0001
All-cause mortality at day 60	29 (21%)	50 (36%)	−15·3% (−25·9 to −4·9)	0·0047
ICU mortality	26 (19%)	43 (31%)	−12·5% (−22·4 to −2·3)	0·0166
Hospital mortality	33 (24%)	50 (36%)	−12·5% (−22·9 to −1·7)	0·0235
Actual duration of mechanical ventilation in ICU survivors, days	14·2 (13·2)	19·5 (13·2)	−5·3 (−8·4 to −2·2)	0·0009
Actual duration of mechanical ventilation in survivors at day 60, days	14·3 (13·3)	20·2 (14·0)	−5·9 (−9·1 to −2·7)	0·0004
Adverse events and complications*				
Hyperglycaemia in ICU	105 (76%)	97 (70%)	5·2% (−5·2 to 15·6)	0·33
New infections in ICU	33 (24%)	35 (25%)	1·6% (−8·5 to 11·7)	0·75
Barotrauma	14 (10%)	10 (7%)	2·8% (−4·0 to 9·8)	0·41

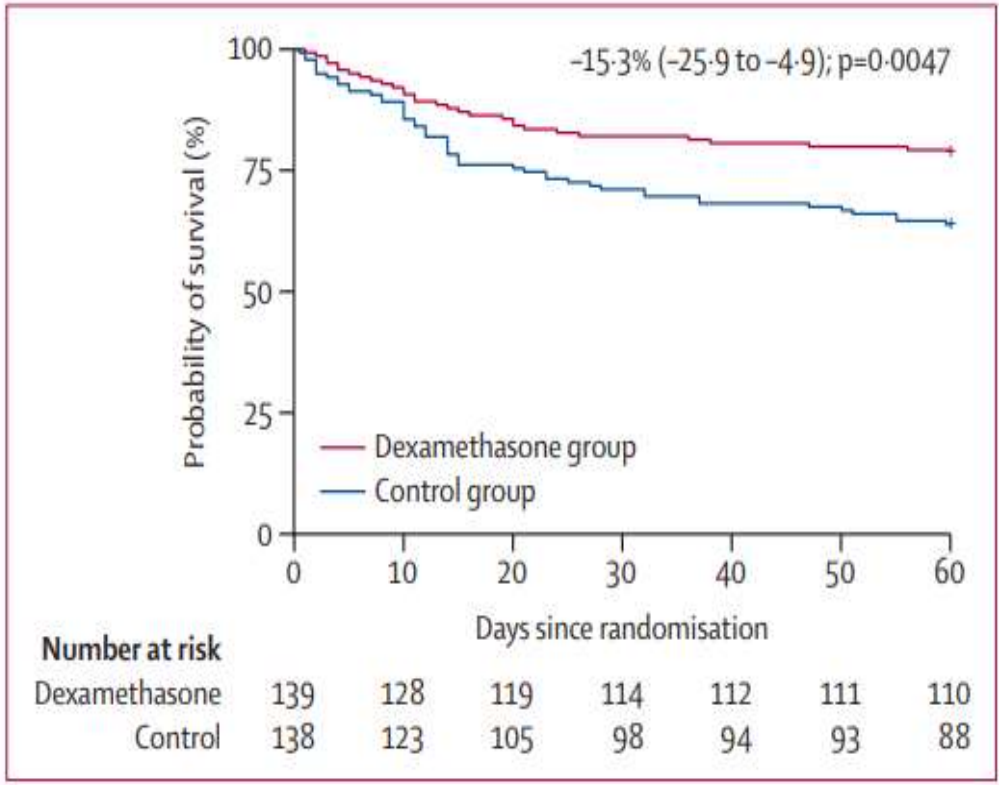


Figure 2: **Kaplan-Meier survival estimates during the first 60 days of trial**

Villar, J. et al. (2020) "Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial," The Lancet. Respiratory medicine, 8(3), pp. 267–276. doi: 10.1016/s2213-2600(19)30417-5.

Safety and efficacy of corticosteroids in ARDS patients: a systematic review and meta-analysis of RCT data -2022

- Fourteen RCTs (n=1607) were included for analysis
- Corticosteroids were found to reduce the risk of death in patients with ARDS (relative risk (RR)=0.78, 95% confidence interval (CI): 0.70–0.87; P<0.01)
- No significant adverse events were observed, compared to placebo or standard support therapy

Xinyang chang et al 2022

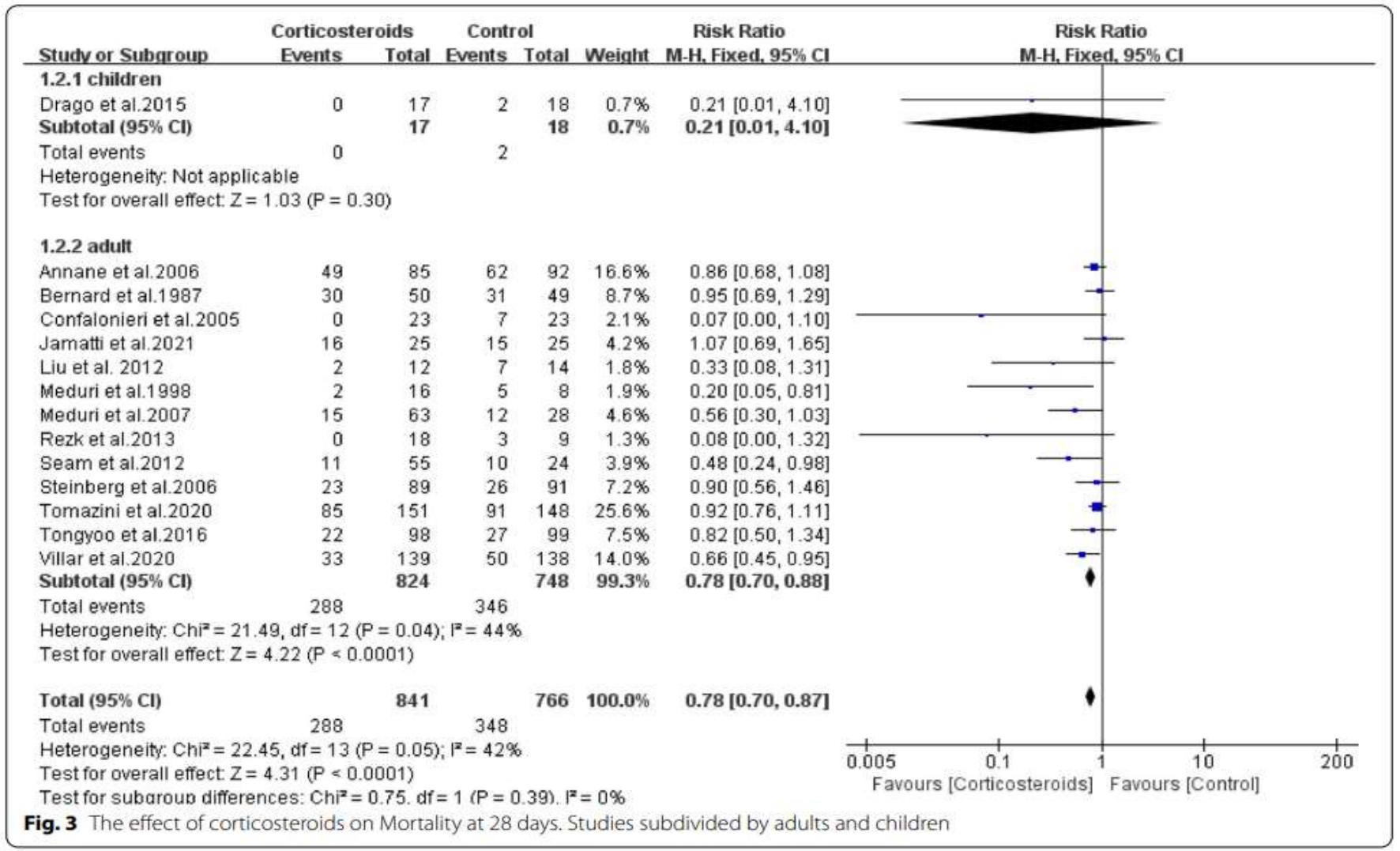


Fig. 3 The effect of corticosteroids on Mortality at 28 days. Studies subdivided by adults and children

Xinyang chang et al 2022

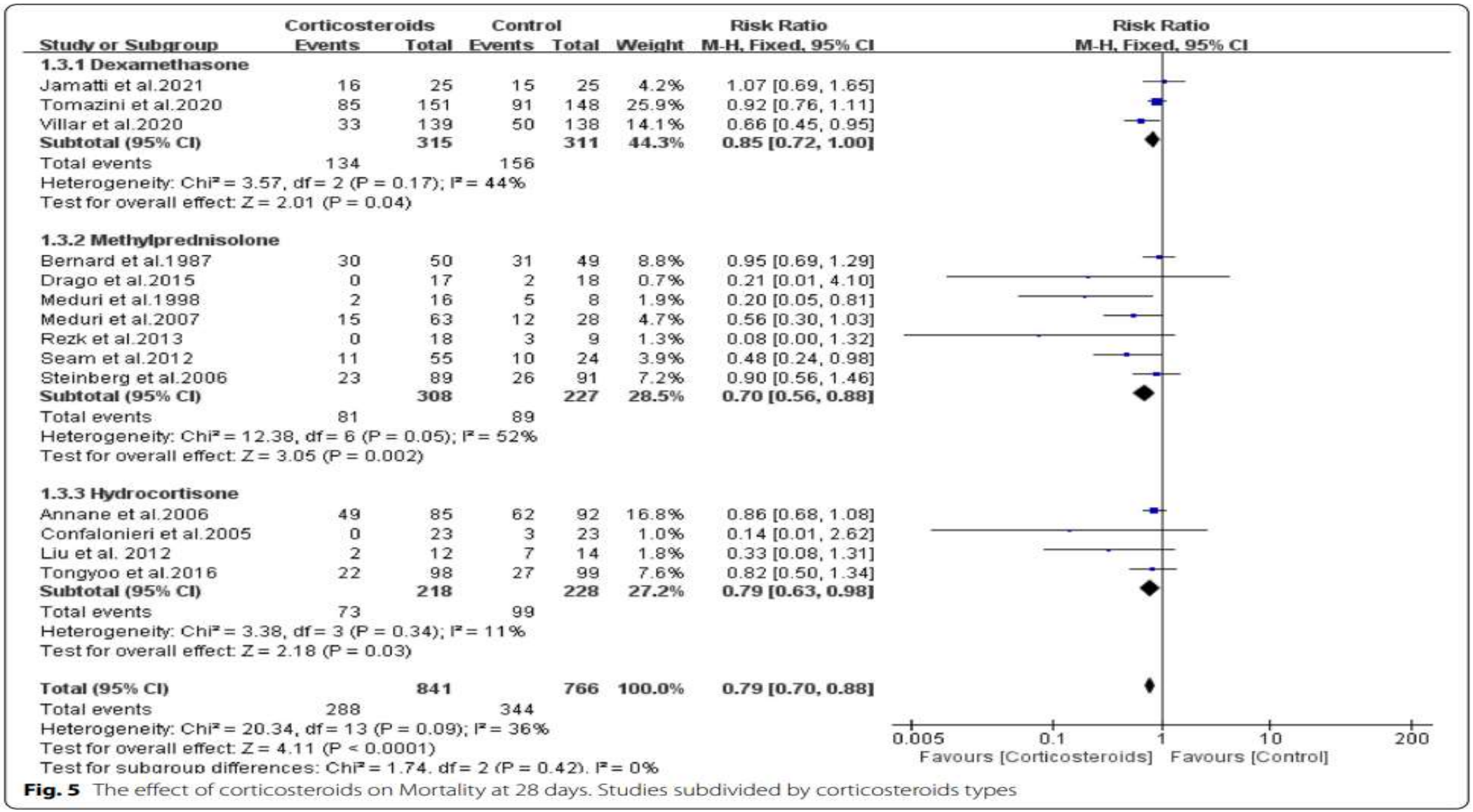


Fig. 5 The effect of corticosteroids on Mortality at 28 days. Studies subdivided by corticosteroids types

Xinyang chang et al 2022

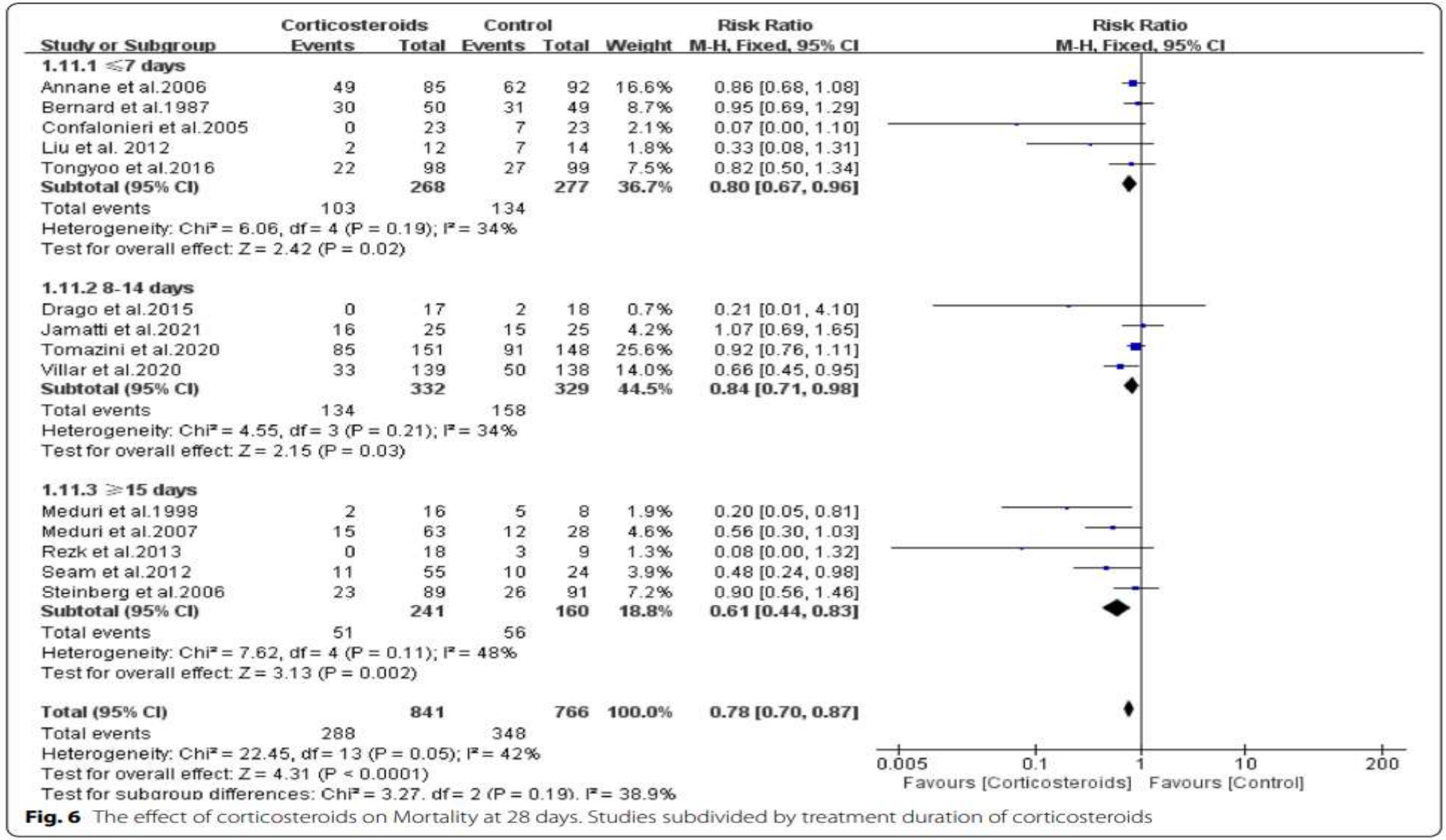


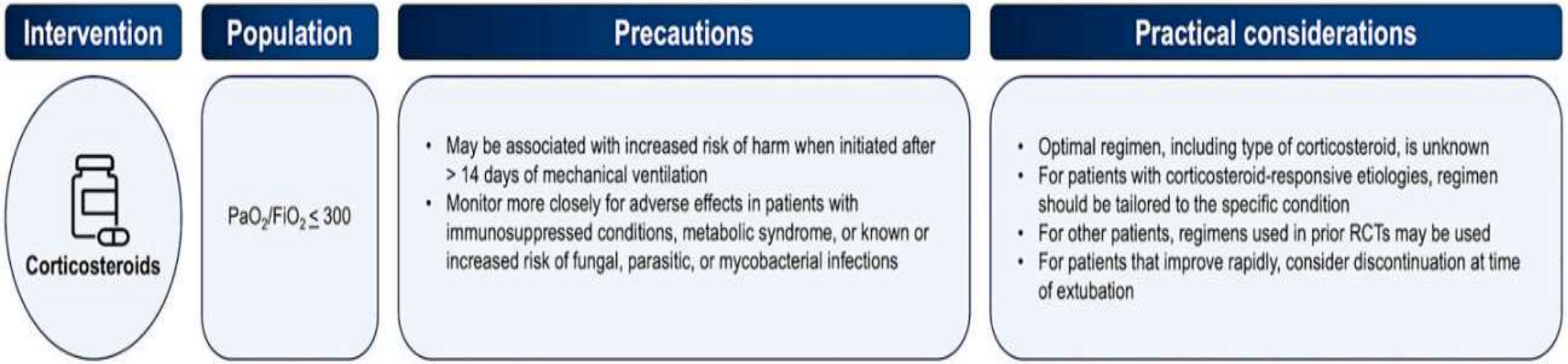
Fig. 6 The effect of corticosteroids on Mortality at 28 days. Studies subdivided by treatment duration of corticosteroids

Role of corticosteroids in ARDS

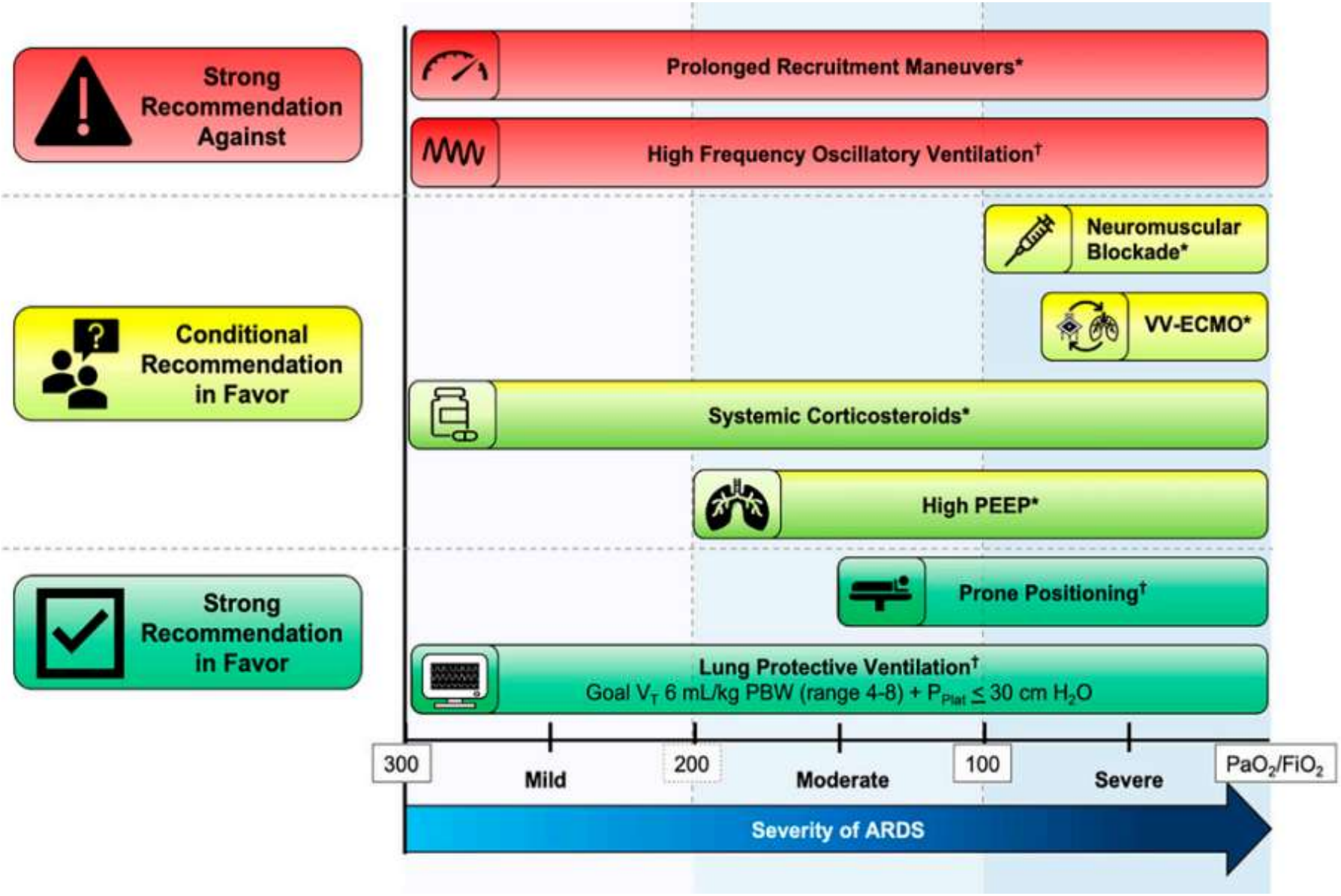
- Corticosteroid use may be an effective approach to reduce death in ards - although empirical use of glucocorticoids remains controversial
- Questions still remain regarding the dosage, optimal corticosteroid agent, and treatment duration in patients

ATS guidelines on ARDS 2024

We suggest using corticosteroids for patients with ARDS (conditional recommendation, moderate certainty of evidence)



(Qadir *et al.*, 2024) "An update on the management of adult patients with ards:, 209(1), pp. 24–36. doi: 10.1164/rccm.202311-2011st.



(Qadir *et al.*, 2024) "An update on the management of adult patients with ards:, 209(1), pp. 24–36. doi: 10.1164/rccm.202311-2011st.

Summary

- New definition is more liberal and overcome the drawback of underdiagnosis of ARDS
- Categorising ARDS into different phenotypes – ray of hope ->might help in better management of ARDS/ identifying specific pharmacotherapy for ARDS
- HFNO – can be used to prevent intubation
- CPAP/NIV role in COVID 19 with AHRF – controversial
- Low tidal volume ventilation

- Higher PEEP without lung recruitment maneuvers (LRMs)
- Prolonged RM to be avoided
- Brief RM – need strong evidence
- Personalized PEEP strategy
- Proning to be done early after intubation in mod – severe ARDS

- NMB can be consider in severe ARDS - 1st 48 hrs
- ECMO to be considered as effective rescue strategy in severe ARDS if worsening despite optimization all ventilatory strategies
- Steroids
- Newer therapies like stem cell-based therapy – need further evidence

Thank You !